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MAJOR CHANGES IN THE FUNDAMENTAL RELATIONSHIPS OF THE RESPIRATORY DRIVE MECHANISMS DURING EVIPAL AND PENTOTHAL ANESTHESIAS, WITH SPECIAL CONSIDERATION OF POSSIBLE APPLICATIONS TO TRANSPLEURAL SURGERY

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WITH the decade just past the medical profession, especially the surgeon, has become particularly interested in respiratory changes associated with the anesthetic state. We have gradually grown conscious of the fact that anesthesia influences the fundamental control mechanisms of respiration in some manner, although little specific knowledge is available to aid us in the establishment of principles upon which an objective choice of an anesthetic agent might be made.

In an attempt to learn a little that might enable one to make a more objective choice, a comparative study of the effects of the common general anesthetic agents upon the respiratory drive mechanisms has been undertaken. Some knowledge has been gained which may ultimately prove to be of fundamental clinical import.

The choice of experimental procedures, which must of necessity be limited in any one series of experiments, has been made upon the following fundamental concepts of respiratory control.

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1. The respiratory center lies in the reticular grey substance of the medulla[20] and is physiologically, but not anatomically,[3] divisible into inspiratory and expiratory centers.[8] Pitts, Magoun, and Ransom[22] have recently reported anatomical divisions of the centers in the cat. Brookhart has not been able to substantiate these findings in the dog. The center is automatically rhythmical and is thereby not directly dependent upon reflex drives for its primitive action.[2]

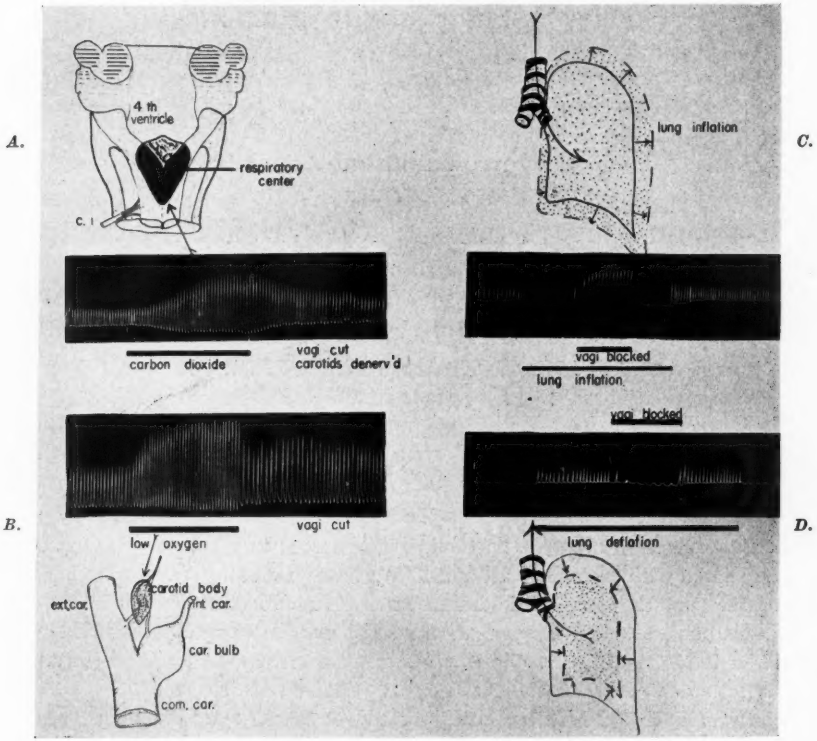
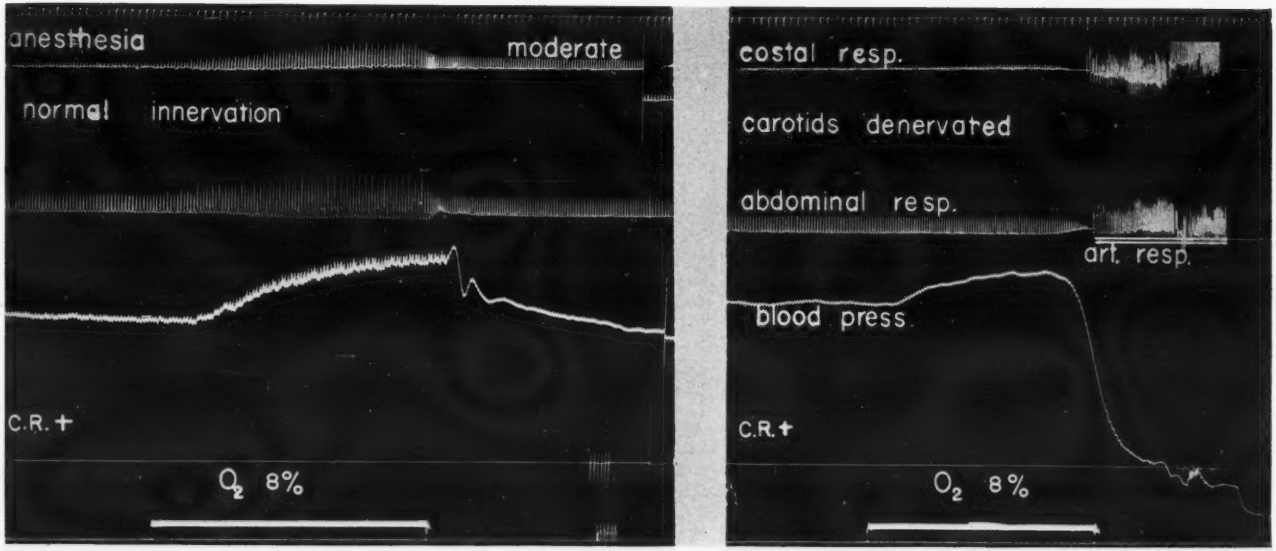


Fig. 1.—*A*, Carbon dioxide—both vagi cut and carotids denervated. *B*, Low oxygen—both vagi cut. *C*, Lung inflation with a short period of bilateral vagal cold block during the inflation. *D*, Lung deflation with a short period of bilateral vagal cold block during the deflation.

2. In the normal, unanesthetized, resting dog or man, breathing is adjusted to a level which effects the removal of carbon dioxide at a rate that maintains the hydrogen-ion concentration of the blood and tissues at a remarkably constant value. The extreme sensitivity of this system can be judged from Haldane's finding that in man an increase of 0.2 per cent or 1.5 mm. in the alveolar carbon dioxide pressure results in a 100 per cent increase in the alveolar respiration, the subject being at rest.[15] The assumption that this fineness of control is primarily of central origin in the intact unanesthetized animal is less tenable today than it was before Heymans discovered the peripheral respiratory chemoreceptor mechanisms (aortic, 1924-27; carotid, 1930-32).[19] The opinions of the foremost men in the field of respiratory physiology differ widely as to the relative roles played by the central and peripheral chemoreflex mechanisms in the control of respiration by carbon dioxide. Schmidt[24] believes that the unanesthetized center is alone capable of effecting this control and



A. *B.*

Fig. 2.—Low oxygen before and after bilateral carotid denervation.

that the carotid and aortic receptors are primarily mechanisms which come into play only when the center is depressed; he has therefore termed the chemoreceptors the *ultimum moriens* of respiratory control. At the opposite extreme are Heymans and his co-workers, who believe that the chemoreceptors may be more sensitive to carbon dioxide than the center and therefore anticipate the respiratory chemical alterations necessary to excite the center and thus prevent possible damage to it that might result from the degree of change necessary for central excitation. Gesell and his associates[10] have concluded from a most ingenious series of experiments that increased ventilation, associated with a slight rise in alveolar carbon dioxide, represents the summation of the chemoreceptor and the central response to hypercapnia but that the response to percentages of carbon dioxide above 6.5 per cent is, as far as can be ascertained, of central origin alone. Fig. 1*A* illustrates central stimulation of breathing that attends the administration of 10 per cent carbon dioxide in an animal lightly anesthetized with evipal. The cervical vagi had been cut, and the carotid sinus regions had been denervated. Because the primary responsibility for hypercapnic hyperpnea produced by a small increase in alveolar carbon dioxide cannot at the present time be termed a complete function of either the central or chemosensitive mechanisms, we have chosen to administer a mixture of sufficiently high carbon dioxide content to assure a maximal stimulation of respiration which for practical purposes may be considered as being due to stimulation of the center.

3. The adequate respiratory adjustment effected by the normally innervated animal anesthetized by any agent when subjected, within fairly wide limits of tolerance, to decreased partial pressures of oxygen in the inspired air is due primarily to increased carotid and aortic body activity.[5] Fig. 1*B* shows the type of respiratory stimulation of carotid reflex origin induced by an oxygen deficiency. Even though the center was also subjected to the hypoxemia, it could not have been directly responsible for any great part of the stimulation as the center of an animal devoid of chemoreceptor afferent nerves and anesthetized with a barbiturate to a level permitting surgery when subjected to similar conditions is incapable of reaction adequately and as a consequence respiratory and vasomotor activity very shortly cease and the animal dies. (Compare *A* and *B* of Fig. 2.) It is evident in Fig. 1 (lower left) that the response to excitation of the chemoreceptors by low oxygen is preponderantly inspiratory. When an increase in expiratory activity is produced, the inspiratory stimulation is always greater.[9] The chemoreceptors therefore serve to some extent as peripheral respiratory half-centers of which the inspiratory is the predominant one.

4. Proprioceptive reflexes (vagopulmonary and somatic-muscular) are capable of modifying the respiratory act in certain specific directions.

A. Vagopulmonary (Hering-Breuer)[17] Reflexes

These reflexes are incited by a change of lung volume and not by alterations in intrapulmonary pressure.[8] Inflation of the lungs during eupneic breathing under moderate evipal anesthesia (Fig. 1*C*) slows breathing by prolonged expiration. Blocking the vagus nerves with cold immediately breaks the expiratory apnea and the chest passively inflates as shown by the inspiratory progression of the respiratory record; when the blocks are removed while the lungs are still inflated, the powerful, prolonged, expiratory effort is reinstated. Lung inflation exerts an inspiratory stimulating action besides its predominant expiratory effect[8, 13]; this is not illustrated here.

Deflation of the lung stimulates breathing as illustrated in Fig. 1*D*. The animal was deeply depressed by evipal and 100 per cent oxygen and was breathing only once a minute. When the lungs were deflated, a normal type of breathing was

established. Blocking the vagi stopped breathing; deblocking was followed by reinstitution of breathing that again returned to a very slow rate on terminating the deflation. Deflation also has a dual excitatory effect; besides stimulating inspiration as here shown, it stimulates expiration to a lesser degree.[14]

It appears at the present time that the afferent impulses of pulmonary origin set off by inflation and deflation of the lungs are excitatory in nature and that any apparent inhibition of breathing is not of direct afferent origin but is a reciprocal function of the primary respiratory motor neurones. For a detailed discussion consult Gesell.[8, 13]

B. Respiratory Muscle Proprioceptors

There is no doubt that these reflex mechanisms play a definite role in respiratory control, though it is as yet indeterminate. The work of Coombs and Pike,[6] Hess,[18] Fleisch,[7] Worzniak and Gesell,[25] and Gesell and Moyer[14] roughly indicates that they predominantly act in a manner similar to, and in conjunction with, the vagal drive reflexes.

C. Vascular Proprioceptive

The most important respiratory reflex of this type has its origins in the carotid sinus and aortic knob. A rise in systemic blood pressure decreases the rate and amplitude of breathing.

METHODS

Mature, healthy, mongrel dogs of both sexes, of varied ages, and of a weight varying between 7.5 and 14 kilograms were used in experiments with evipal (50 mg. per kilogram, in a 10 per cent aqueous solution) administered intravenously; in the other series pentothal (25 mg. per kilogram in a 5 per cent aqueous solution) was given in the same manner. The anesthesia was thereafter maintained or varied at will by additional injections or withholding of the drug used. No preanesthetic medication was employed.

The depth of the anesthesia was followed objectively throughout the experiment. The ipsilateral sciatic reflex contraction of the left semitendinosus muscle was recorded. The stimulus was maximal and was provided by a Harvard inductorium; only break shocks were employed. A mercury-platinum contact key was used to make and break the primary circuit. The lid and corneal reflexes were observed. A quick, sustained response to a fairly constant stimulus was recorded as ++; a reflex that was obtainable only on repetitive stimulation or that fatigued quickly was designated as +.

Tidal air was recorded with a Hutchinson spirometer. The spirometer and the external Tisot valved circuit were connected through brass steam valves to three interconnected 60 liter steel tanks. This arrangement allowed almost instantaneous changing from one rebreathing mixture to another without disturbing the animal. Lung volume changes (inflation and deflation) were produced by weighing and counterweighing the spirometer to make the intrapulmonary pressure 70 mm. of water above and below atmospheric pressure, respectively.

Carbon dioxide was routinely absorbed by fresh soda lime except during carbon dioxide administrations when the absorption cartridge was cut out of the circuit.

Respiratory movements of the chest and abdomen were recorded, using encircling paper bands in a manner similar in principle to that described by Gesell and Moyer.[11]

The end mean blood pressure in the femoral artery was routinely recorded with a mercury manometer (Ludwig type).

Time in five-second intervals constitutes the top line in all records.

The animals were constantly connected to the rebreathing system and breathed room air (O_2 21% ± 1%, CO_2 0.05 → 0.08%, and N_2) during the "normal" periods.

The carbon dioxide mixtures were made up to contain not less than 26 per cent and not more than 29 per cent of oxygen.

Inspiration is up in all respiratory records.

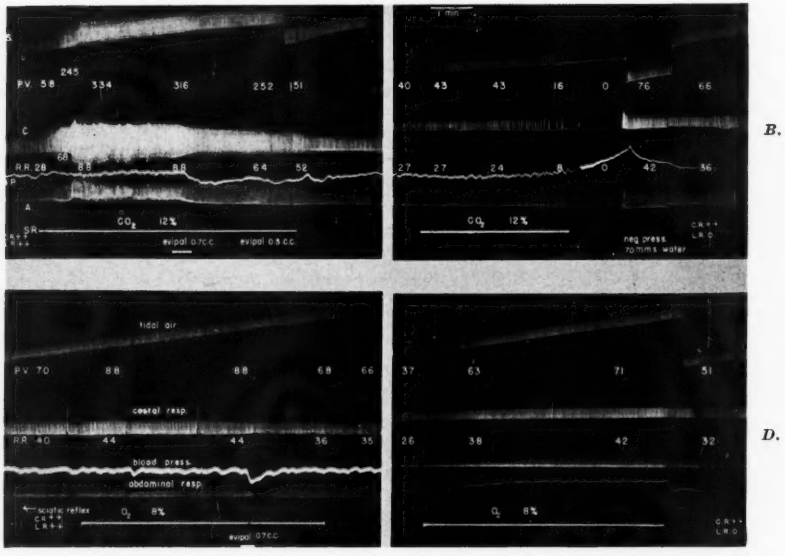


Fig. 3.—High carbon dioxide and low oxygen administration during light and moderate evipal anesthesia. *S.*, Tidal air. *P. V.*, minute volume of breathing in deciliters per minute; *C.*, costal breathing; *R. R.*, rate of breathing per minute; *B. P.*, blood pressure; *A.*, abdominal breathing; *C. R.*, corneal reflex; *L. R.*, lid reflex; *S. R.*, sciatic reflex.

RESULTS

What effects have evipal and pentothal* upon the major respiratory drive mechanisms, namely, upon the central, the chemoreceptive, and the vagopulmonary proprioceptive? Fig. 3 affords a comparison of the effects that the deepening of evipal anesthesia has upon the central chemical drive (carbon dioxide) and upon the peripheral (carotid and aortic) reflex chemical drive (low oxygen) in the same animal. The anesthesia was light when sections *A* and *C*, and moderate (roughly equivalent to stage iii, plane i of ether anesthesia) when sections *B* and *D* were obtained. It is clear that increasing the depth of the narcosis changed the response to 12 per cent carbon dioxide from an intense stimulation of breathing to a very minor initial stimulation that was followed by a serious depression of respiration as shown by the cessation of breathing and asphyxial rise in blood pressure (*B*). Deepening the

*The effects of pentothal upon the respiratory mechanisms are, in general, qualitatively similar to those produced by evipal; the duplication of illustrations was therefore not considered to be necessary.

anesthesia, however, actually accentuated the response to oxygen deficiency. Under light anesthesia (*C*) minute volume increased 1.8 liters, and the respiratory rate, 4 per minute; under moderate anesthesia (*D*) minute volume increased 3.4 liters per minute, and the rate, 16 per minute. This is not an unusual finding in this series of experiments and will be dealt with later in greater detail.

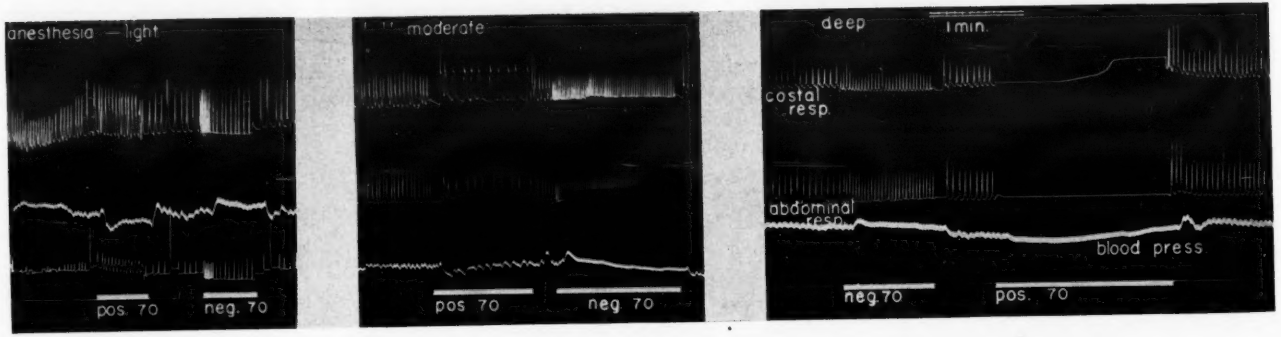
Increasing depth of evipal and pentothal anesthesias as a general rule affects the Hering-Breuer (vagopulmonary) reflexes as illustrated in Fig. 4. A lightly anesthetized animal (left) reacts to lung inflation (pos. 70) and lung deflation (neg. 70) by a very transient slowing and speeding, respectively; when moderately anesthetized, he responds to inflation by a well-sustained, more pronounced slowing and to deflation by a well-maintained, equivalent acceleration. When deeply anesthetized, he reacts to the same procedures respectively by an expiration of two minutes' duration, the length of time the lungs were inflated, and by a lesser but well-sustained speeding of breathing.

It is therefore apparent that the anesthesia produced by evipal and pentothal, when carried to a depth equivalent to stage iii, plane i, of ether profoundly depresses the central response to carbon dioxide upon which a great part of the regulation of normal breathing and acid-base equilibrium depends but effects a relatively slight depression of the reflex drives, chemical (carotid) or proprioceptive (vagal). Breathing under moderate evipal and pentothal anesthesia is therefore very likely to be largely or even entirely dependent upon reflex drives for its maintenance. Any reduction of these reflex drives is likely to result in respiratory failure as illustrated in Figs. 5 and 6.

Under moderately deep anesthesia (Fig. 5), when the breathing mixture was changed from room air to 100 per cent oxygen, the dog's breathing gradually slowed and finally stopped. A long period of artificial respiration and readministration of room air was necessary to reinstitute breathing. The rise in arterial oxygen tension that followed the increase in oxygen tension of the inspired gas evidently effected a reduction of the carotid and aortic reflex chemical drive that, in the absence of an adequate central chemical drive (carbon dioxide), resulted in respiratory failure.

Fig. 6, left, illustrates the effect of removing the vagal drive during light, moderate, and deep evipal anesthesia. As the anesthesia was deepened, the slowing of breathing that followed blocking the vagi with cold increased. The slowing was so great under deep anesthesia that the animal died. This has not occurred when cyclopropane or ether were used as the anesthetic agents because the slowing effect of vagal block progressively decreases as the depth increases under these agents as shown on the right and lower center of Fig. 6.

Evipal and pentothal therefore cannot be considered as safe anesthetics in that they are capable of completely suppressing a major drive



A. *B.* *C.*

Fig. 4.—Lung inflation (pos. 70) and lung deflation (neg. 70) during light, moderate, and deep evipal anesthesia.
Pos. 70, lung inflation } by a force equivalent to 70 mm. H_2O pressure.
Neg. 70, lung deflation }

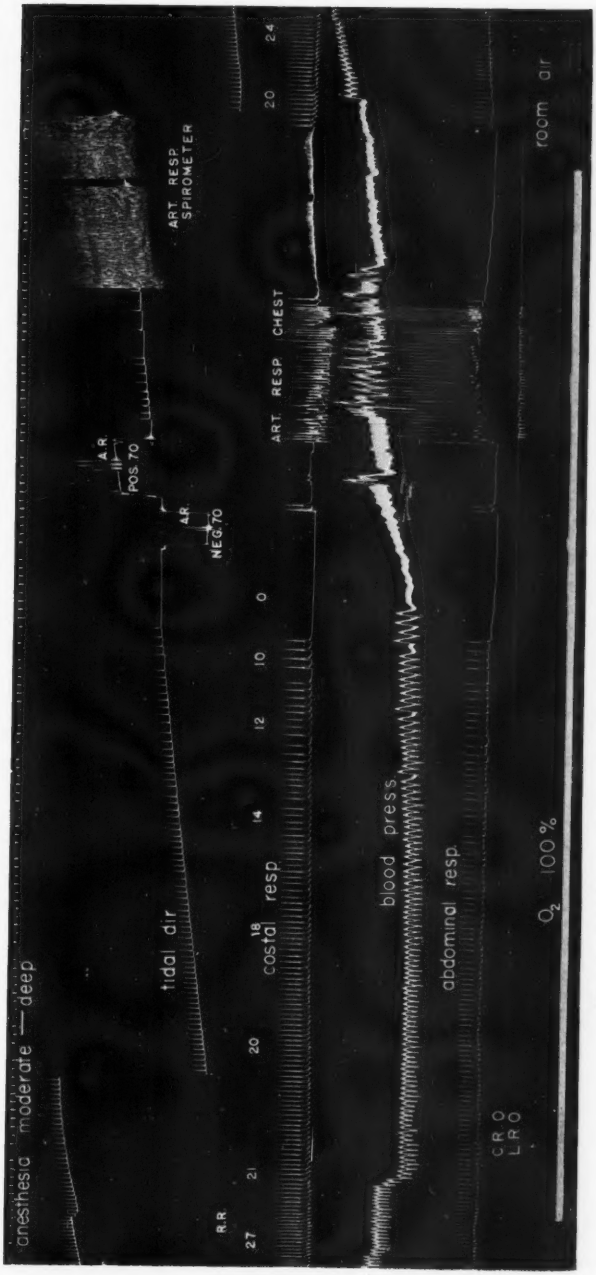


Fig. 5.—Inhalation of 100 per cent oxygen under moderately deep evipal anesthesia.

of breathing, the central chemical drive, while effecting relatively little depression of the reflex drives at a level of anesthesia that in many instances will not permit the performance of major surgery. They are

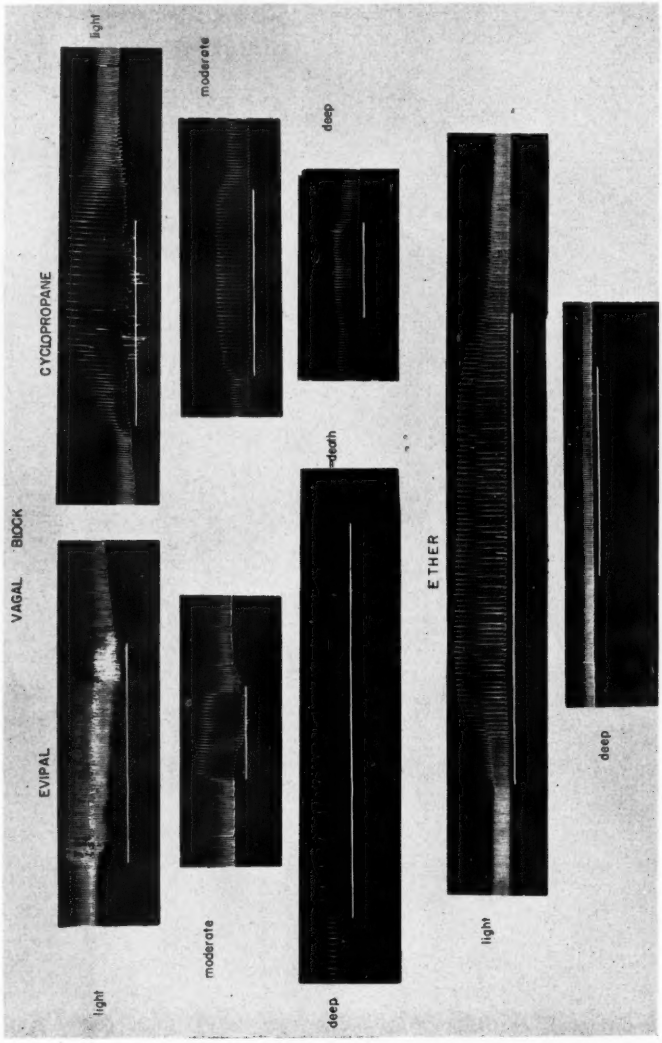


Fig. 6.—Bilateral vagal cold block under light, moderate, and deep evipal and cyclopropane anesthesias, and under light and deep ether anesthesia. Solid horizontal bars indicate the duration of the block.

less safe should the surgery being done make it necessary to open the pleural cavity as this immediately upsets the balance struck between the center and the proprioceptive respiratory reflexes and interferes appreciably with gas exchange in the lungs. The interference with gas

exchange results in varied degrees of oxygen lack and carbon dioxide excess. How do these conditions affect the respiratory depressant action of these anesthetics?

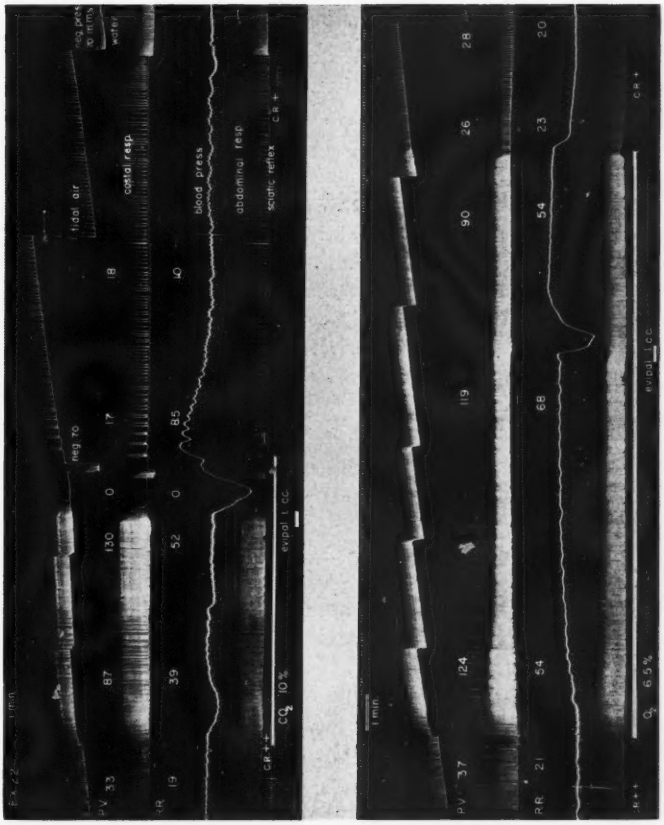


Fig. 7.—The intravenous injection of evipal during high carbon dioxide and low oxygen administrations under light anesthesia.

Part of the answer to this question is to be found in Experiment 22 (Fig. 7). When evipal was given during the hyperpnea produced by the inhalation of carbon dioxide, the rate and amplitude of breathing rapidly diminished and minute volume fell from 13 liters per minute to zero. During the apnea a short period of lung deflation was associated with an excellent deflation vagopulmonary reflex response, especially, an inspiratory progression of the abdominal respiration and a fast rate of breathing. Ventilation gradually increased after termination of the carbon dioxide inhalation.

After a twenty-minute rest the same amount of evipal was given at the end of ten minutes of hypoxic hyperpnea and the low oxygen administration continued for another 5.5 minutes after the evipal was

given. Minute volume fell 2.9 liters per minute. However, a 5.3 liter increase over the preanoxic ventilation remained until the hypoxia was terminated. Following recovery from the anoxia another 1 c.c. of evipal was given while the animal breathed air (not illustrated); minute volume of breathing decreased from 3.3 liters to 2.4 liters per minute. By comparing the breathing before low oxygen in Fig. 5 with that after it, a qualitative picture may be constructed that is practically identical to that present when the evipal was given during eupnea.

These qualitative reactions have been substantiated in seven experiments under evipal and five under pentothal. There is, therefore, but little doubt that carbon dioxide excess accentuates the respiratory depressant action of these anesthetics and that oxygen deficiency masks it when the animal is lightly anesthetized. The picture is different when the drug is injected during hypoxemia that is induced while the animal is deeply anesthetized (stage roughly comparable to stage iii, plane ii, of ether). Then a very much more severe respiratory depression is produced than when the same amount of drug is given while the animal breathes room air. This depression is frequently irreversible in spite of all attempts at resuscitation. This phenomenon is being described more fully by Beecher and Moyer in a separate communication. In brief, these reactions have been interpreted to mean that the well-known central depressant action of hypoxemia and the similar actions of the barbiturates are additive in spite of the apparent contradictory evidence obtained during light anesthetic states.

The disturbance of the balance between the central and chemosensitive reflex drives and the proprioceptive reflex drive that obtains when the pleural cavity is opened also introduces dangers that are not present when the chest is intact. Any diminution in size of lung, as is usually present during transpleural operations, stimulates breathing *when a barbiturate is employed as an anesthetic.* Inasmuch as the deflation reflex stimulation of breathing is not readily depressed by these agents, an overdose of evipal or pentothal may be given during the period that the lungs are smaller than normal without any appreciable diminution in breathing; only when the deflation drive is interrupted either by cutting or blocking the vagus or by re-expansion or removal of the lung will the true state of affairs become apparent. Breathing may continue either normally or abnormally or it may stop as it did when the deflation was terminated in the experiment shown in Fig. 1, lower right. This danger is not nearly so imminent when ether or cyclopropane is employed. Inflation and deflation of the lung have very little effect on the rhythm of breathing at any depth of ether or cyclopropane anesthesia (Fig. 8).

With the chest open it is often necessary to keep up a positive pressure in the airway to stabilize the mediastinum and thus maintain some semblance of normal respiratory exchange. Should this pressure be

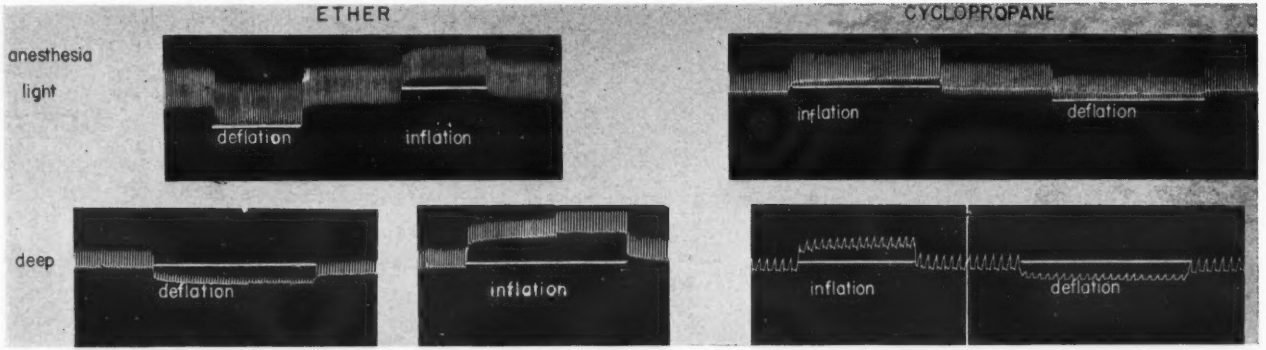


Fig. 8.—Lung inflation and deflation (pos. and neg. 70 mm. H_2O) under light and deep ether and cyclopropane anesthesia.

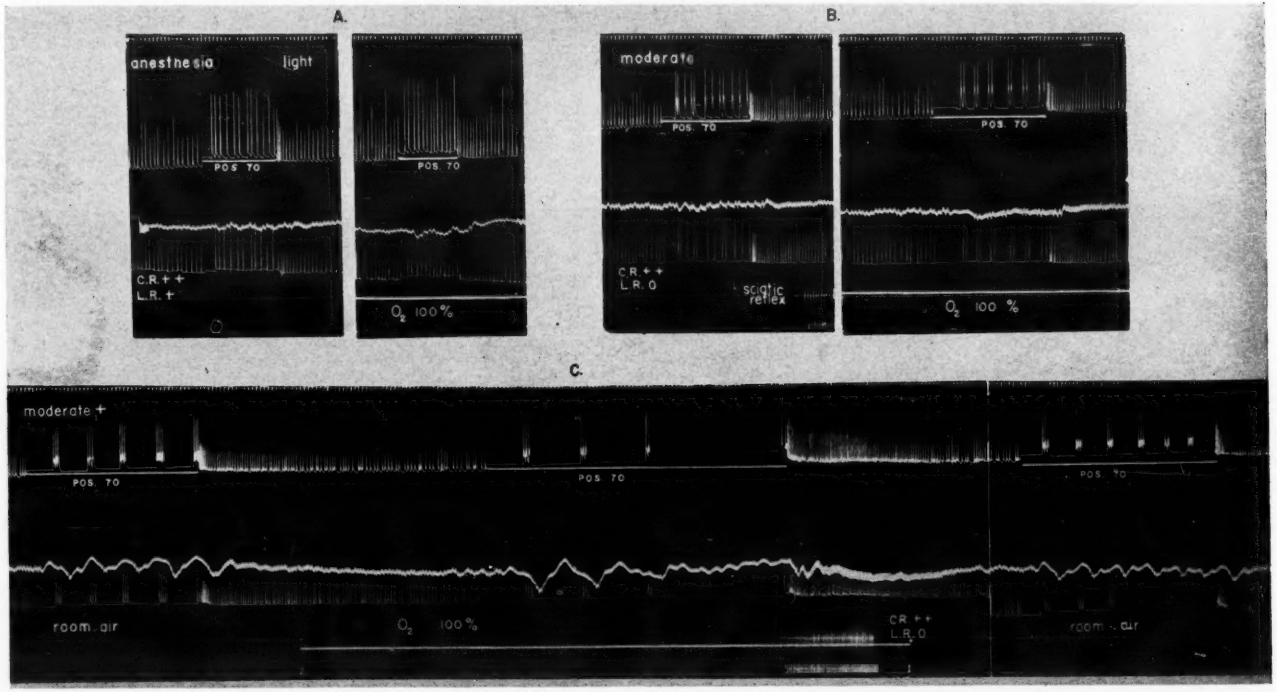


Fig. 9.—Lung inflation during the inhalation of room air (not designated by bar) and 100 per cent oxygen (solid horizontal bar) under light, moderate, and moderate + evipal anesthesia.

great enough to expand either lung enough to bring into operation the inflation Hering-Breuer reflex, breathing will be slower than the rate dictated by oxygen need or carbon dioxide excess. Cyanosis might then appear, and high oxygen may be given to combat the cyanosis. Breathing then slows more if the anesthesia is moderate as in Fig. 9*B*, or stops if the anesthesia is deep (Fig. 9*C*). Without the administration of high percentage of oxygen the breathing is slower than normal when the lungs are inflated (left and right sections of Fig. 9*C*) but it does not become progressively slower as it does when 100 per cent oxygen is breathed (middle section of Fig. 9*C*). Note that, when 100 per cent oxygen is breathed while the lung volume is normal, breathing slows moderately (Fig. 9*C*). These possibilities of getting into difficulty are not to be expected with cyclopropane or ether.

DISCUSSION

The material presented shows that certain important changes occur in the integration of the driving forces of breathing whenever evipal or pentothal is used as an anesthetic agent. From a fundamental standpoint the most important change is the profound depression of the stimulant action of carbon dioxide. Sixty-six per cent (eight out of twelve) of the animals anesthetized with evipal and 11 per cent (one out of nine) of those anesthetized with pentothal demonstrated the change at a stage of anesthesia either lighter than, or roughly equivalent to, stage iii, plane ii, of ether anesthesia. Yandell Henderson[16] has long recognized this property of the barbiturates and has recently coined the term anarchapnia to designate the state in which the center no longer is stimulated by carbon dioxide. Marshall and Rosenfeld,[21] and Schmidt[24] have also found that barbiturates with and without morphine produce this effect.

In this series of experiments it has been found that evipal and pentothal without morphine will produce the state of anarchapnia at a level of anesthesia in which the corneal and sciatic reflexes are active and respiration can be driven very effectively by reflex stimulation, proprioceptive and chemosensitive. In fact comparable degrees of pulmonary deflation and hypoxemia often produce a greater increase in the respiratory exchange under deep anesthesia than under light anesthesia (Fig. 3, low oxygen, and Fig. 4*B*, deflation).

Since a large part of the regulation of breathing and acid-base balance depends upon the respiratory center's ability to respond to carbon dioxide, the maintenance and regulation of these two very important biologic reactions in the anarchapnic state are placed largely upon the chemosensitive reflex mechanisms. This statement previously set forth by Marshall, Schmidt, Rovenstine, and others is held to be true for evipal and pentothal upon the basis of the present experiments.

Are the chemosensitive reflex mechanisms as capable of discharging this responsibility as is the normal or lightly anesthetised center? Obviously not, at least in anesthetic states, for a mechanism cannot be considered adequate when it fails to effect breathing adjustments to an increase in carbon dioxide within the body (Fig. 3*B*) although it shows by its response to an oxygen deficiency (Fig. 3*D*) that its effectiveness apparently has not been very greatly impaired. Unscientifically stated, the carotid and aortic bodies of narcotized animals are seemingly solely interested in keeping their oxygen supply adequate for their own metabolism and will drive the unresisting (depressed) respiratory center toward this end without consideration for the oxygen need or acid-base balance of the rest of the body.

Therefore, should one elect to anesthetize an animal, including man, with evipal or pentothal sufficiently deeply to allow the performance of major surgery, he must accept the risk of changing the control of breathing and of the acid-base balance in an unpredictable manner. This risk is great with an intact chest but is very much greater should the pleural cavity be opened, as the partial or full collapse of a lung interferes more or less with gas exchange and permits the development of varied degrees of hypoxemia and hypercapnia. Both of these conditions accentuate the respiratory depressant action of these drugs.

The disturbance of the balance struck between the center and the proprioceptive reflex mechanisms introduces other dangers. The institution of the deflation vagopulmonary reflex by reduction of lung size institutes a drive of breathing that is not greatly affected by the anesthetic; consequently, respiration cannot be relied upon as an indication of anesthetic depth or the status of the respiratory center. Any evipal or pentothal given during the time that a lung is smaller than normal is therefore given blindly; termination of the deflation by reinflation of the lungs or severance of the afferent pathway by blocking or cutting the vagus may result in respiratory failure as illustrated in Fig. 1*D*, and Fig. 6 (evipal anesthesia).

If the inflation vagopulmonary reflex becomes operative, the dangers that attend hypoxemia and hypercapnia become intensified. Should a high concentration of oxygen be breathed while this reflex is predominant, breathing may well fail acutely (Fig. 9*C*). The dangers discussed in the last paragraph are relatively small under cyclopropane or ether anesthesia, as proprioceptive reflex drives under these agents do not effect any great change in the rhythm of breathing. Consult Fig. 8.

The dangers inherent in evipal or pentothal anesthesia that are made imminent by opening the chest seemingly rest upon the fact that the chemical drive (carbon dioxide) of the center is much more rapidly depressed by these drugs than are the reflex drives. Because we have no means of judging by respiratory, circulatory, or reflex signs as to when the center's chemical drive is sufficiently reduced as to cause the control

of breathing to slip from the control of the center to that of the primitive reflex drive mechanisms (Figs. 3 and 5), the use of these short acting barbiturates should be far more restricted in thoracic surgery than in surgery of other regions. In fact, the use of the barbituric acid derivatives for all types of major surgery in man should be limited to an absolute minimum until such a time as a more complete study may yield exact information about the safety limitations of these anesthetic agents, or until such time as comparable work on human beings may have shown that the findings in dogs cannot be transposed to man.

Should these agents be used, a greater number of respiratory failures must be anticipated than would occur with well-controlled ether anesthesia. The experimental work presented here establishes a few basic principles upon which resuscitation measures should be based. It will be obvious that the measures recommended are not exactly those that have been found most effective in combating respiratory failure from other causes—anesthetic or otherwise.

Obviously, the inhalation of carbon dioxide in oxygen is very clearly contraindicated. Both gases alone are capable of producing respiratory failure during moderately deep anesthesia with evipal or pentothal (Figs. 3 and 5). Luck alone should be thanked if recovery should take place following the depressing action of a combination of these gases.

The respiratory stimulants such as metrazol, coramine, lobeline, picrotoxin, and caffeine are not to be relied upon. The thing to be done and done immediately is to supply oxygen, in concentrations not too high, and to remove carbon dioxide. The surest and quickest method of effecting these changes is by adequate artificial ventilation with a gas of which the oxygen content is not less than 20 per cent and not more than 40 per cent, and the carbon dioxide is not more than 5 per cent (less of the carbon dioxide may be indicated). However, on the basis of our present knowledge, the best practice is to consider the possibility of acapnia arising as a result of too vigorous artificial respiration and to include 5 per cent carbon dioxide in the gas mixture.

In performing artificial respiration one must consider its effect upon the respiratory center via the pulmonary vagal drive mechanisms, as well as upon the gas exchange within the lung. Any pressure on the chest wall expels gas from the lungs and also brings the proprioceptive deflation drive reflexes into play which will, if they are strong enough, stimulate the inspiratory center and thus hasten the return of spontaneous breathing. (See Fig. 5, *Art. Resp. Chest.*) This experiment affords an opportunity to compare the relative effectiveness of torso pressure artificial respiration with that effected via the airway. Rhythmical pressure upon the chest as shown (*Art. Resp. Chest*) was associated with the resumption of inspiratory activity of the animal, as shown in the tidal air record. After artificial respiration via the air-

way was begun (*Art. Resp. Spirometer*), only one spontaneous inspiration occurred, as shown in the abdominal respiration record. The movements evident in the costal record during artificial ventilation via the airway were entirely passive; no respiratory activity of the animal was evident as long as this type of artificial respiration was carried out, even after room air was administered to the animal. Positive pressure artificial respiration via the airway tends to hyperinflate the lungs and thus stimulate the expiratory center via the inflation pulmonary vagal reflex; this method of artificial ventilation would be far more likely to result in acapnia and a delayed onset of spontaneous breathing. Such positive pressure is, in addition, harmful through compression of the pulmonary vascular bed. However, as it is frequently impossible, inexpedient, or clinically unsound in actual surgical practice to use a torso pressure method, positive pressure artificial ventilation will have to be used in spite of its physiologic inferiority.

Should the chest be open when respiratory failure occurs, artificial ventilation must, of course, be carried on through the airway. Special attention should then be directed toward having the bag only partially filled; this will allow the inspiratory stimulating deflation reflex to become operative when pressure is removed from the bag. An anesthetist who has a working knowledge of the vagopulmonary reflex mechanisms and the pharmacology of the anesthetic agent employed would be far better able to reinstitute normal respiration when the chest is open than when it is closed.

If, by the time artificial ventilation is begun, blood pressure has fallen, 2 to 4 minims of epinephrine should be given and repeated if necessary, as no amount of artificial respiration can effectively remove carbon dioxide from and supply oxygen to the brain unless a fairly adequate volume flow of blood is present (Fig. 2). Schmidt[24] has demonstrated very clearly the respiratory resuscitant power of epinephrine on a respiratory center depressed with morphine, urethane, and 100 per cent oxygen.

SUMMARY

The effects of evipal and pentothal anesthesia upon the respiratory responses of dogs to high carbon dioxide, low oxygen, and changes of lung volume have been studied. Both anesthetic agents depressed the response to carbon dioxide inhalations much more rapidly and profoundly than they did the responses to low oxygen and changes of lung volume. At a level of anesthesia roughly comparable to stage iii, plane ii, of ether anesthesia, the breathing of 66 per cent of the animals anesthetized with evipal and 11 per cent of those anesthetized with pentothal was either depressed or not stimulated by the inhalation of carbon dioxide; however, the stimulating effects of low oxygen and

lung volume changes were still very apparent. At the level of anesthesia at which the response to carbon dioxide was very profoundly depressed and in many instances abolished the reduction of the carotid chemical reflex drive attending the administration of 100 per cent oxygen or the obliteration of the vagopulmonary drive by blocking the vagi frequently induced respiratory failure.

These reactions were not obtained at any stage of ether or cyclopropane anesthesia.

The differential action of evipal and pentothal upon the respiratory drive mechanisms tends to cause an early loss of precise control of breathing and of acid-base equilibrium. They are, therefore, inferior anesthetic agents and should not be used for any but short, relatively atraumatic operative procedures.

It was also found that hypoxemia and hypercapnia accentuate the respiratory depressant action of evipal and pentothal. Inasmuch as these states are clinically likely to be associated with an open pleural cavity, evipal and pentothal are more emphatically contraindicated in transpleural surgery than they are when the thoracic wall is intact.

Should respiratory failure occur during anesthesia produced by evipal or pentothal, artificial respiration, preferably by a torso pressure method, appears to be indicated. If this is impossible, inexpedient, or directly contraindicated, bag pressure must be used, care being taken to have the bag only partially filled and to remove all pressure from it between compressions. The gas mixture administered should contain not more than 40 per cent oxygen and not more than 5 per cent carbon dioxide. If the blood pressure is low before or during the artificial respiration, from 2 to 4 minims of epinephrine should be given intravenously and repeated if necessary.

I wish to thank Dr. H. K. Beecher for his kindness in freely extending to me the facilities of the anesthesia laboratory and for his very valuable help in the conduct of this work.

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DISCUSSION

DR. EDWARD C. CHURCHILL, Boston, Mass.—The maze of leads and suggestive questions that have been proposed by Dr. Moyer make most of us feel we are incapable of discussing this paper. It is evident, however, that vistas are opened that display the complicated mechanisms involved in any intrapleural operation, particularly a total pneumonectomy. When the anesthetist empirically administers carbon dioxide to stimulate respiration, it is well to remember that it may have exactly the opposite effect. When 100 per cent oxygen is administered to an anoxemic patient, it may entirely stop his respiratory movements. A great many practical applications of this investigation will be found in the future of pulmonary surgery.

OBSERVATIONS ON THE EFFECTS OF THE PROLONGED ADMINISTRATION OF HIGH OXYGEN CONCENTRATION TO DOGS

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INTRODUCTION

THE medical use of oxygen shows a continued and as yet unabated increase. The development of the Boothby-Lovelace-Bulbulian (B. L. B.) mask has not only increased the application of this method of treatment but has also made it possible to administer high concentrations of oxygen efficiently and economically. The interest of surgeons has been stimulated by the report of Fine (1935) that the respiration of high concentrations of oxygen (over 80 per cent) is effective in removing accumulations of gas within the body such as occur in the intestines in cases of mechanical or paralytic obstruction.

Both Fine and Boothby advocate "100 per cent" oxygen but have repeatedly warned that the administration of such high concentrations should be interrupted for brief periods several times a day and ordinarily should not be continued for more than forty-eight hours. The reasons for this recommendation have been given in vague statements about "oxygen poisoning."

Despite the considerable amount of investigation which has been carried out on the subject of oxygen poisoning, little is known about it by the medical profession as a whole. It seems fitting, therefore, to draw attention to the possible effects of high oxygen concentrations on the lungs and other organs as observed in a relatively large number of dogs. Previous experimental work has been practically entirely confined to the use of small animals, such as mice, rats, guinea pigs, rabbits, and birds, or to the use of pressures greater than that of the atmosphere. Noteworthy contributions have been made by Bert, 1878; Smith, 1899; Barach, 1926; Binger, Faulkner, and Moore; Binet, Bochet, and Bryskier, 1939. The only report of oxygen poisoning in a human being resulting from a pressure equal to or less than that of the atmosphere,

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with which the author is familiar, is that of Becker-Freyseng and Clamann in 1939.

The purposes of the experiments reported in this communication were (1) to determine the quantitative changes in the oxygen and carbon dioxide content of the gas in the obstructed bowel of dogs incident to the respiration of a high concentration of oxygen and (2) to observe the toxic effects of the prolonged respiration of high concentrations of oxygen on dogs.

EXPERIMENTAL PROCEDURES

For the administration of a high concentration of oxygen, a gas-tight box approximately 3′ by 4′ by 5′ in size was constructed of plywood and glass. The top was hinged at the side and so fitted with a rubber gasket and latches that an airtight seal could be maintained. In the bottom of the box a low platform of lathes was placed above 2 to 3 inches of sawdust and wood shavings which served to absorb the excreta. Along the sides at the top of the box were hung two narrow shallow trays containing soda lime. Other trays were fastened at one end of the box into which water, milk, or other food could be run through rubber tubes leading through the top of the box. When not being used, these tubes were kept closed with stoppers. A refrigerating coil together with a thermostat was installed around the side walls of the box which enabled an internal temperature of between 70 and 80° F. to be maintained. A serum stopper was fitted tightly into a hole in one end of the box so that, when a needle was inserted through it, samples of air could be taken in order to measure the oxygen and carbon dioxide content.

Commercial oxygen was supplied to the box through a flowmeter and differential valve so calibrated that mixtures of air and oxygen in varying proportions could be given as desired. A rubber flutter valve, such as is commonly used in basal metabolism machines, served as an exhaust. The efficiency of this box was such that, if pure oxygen were admitted at a rate of 2.5 liters per minute, an oxygen concentration of 99 to 100 per cent would be maintained.

The dogs used in those experiments in which the oxygen and carbon dioxide content of the intestinal gas was studied were subjected to two operations before being placed in the oxygen chamber. All operations were performed under anesthesia obtained by the intravenous injection of 35 mg. of sodium pentobarbital for each kilogram of body weight. Aseptic surgical technique was used in each operation. As a preliminary procedure, a Biebl loop was constructed by bringing a short loop of either the terminal ileum or descending colon outside the peritoneal cavity and covering it with skin. Such an arrangement allows for repeated aspiration of the contents of the loop by needle and syringe without contamination of the peritoneal cavity.

Two weeks later the ileum or colon of these animals was obstructed immediately distal to the extraperitonealized loop by severing the gut and inverting the cut ends.

At chosen intervals after the production of the obstruction the dogs were placed in the oxygen chamber and the experiments begun. A concentration of oxygen of over 95 per cent was maintained. At intervals the animals were removed from the chamber and small samples of intestinal gas aspirated from the loops. In some of the experiments x-ray films of the abdomen were taken at the start of the experiment and each day thereafter to estimate the increase or decrease in the quantity of the intestinal gas. At the conclusion of each experiment the amount of gas and fluid remaining in the intestine proximal to the obstruction was measured with a syringe at the time of the post-mortem examination.

The dogs used to study the general effects of respiring high concentrations of oxygen were stock animals weighing 15 to 30 pounds each. Usually two animals were placed in the chamber at the same time. In most cases a concentration of oxygen between 95 and 100 per cent was maintained. In some experiments the concentration was maintained between 85 and 90 per cent, however, and in still others it was maintained between 75 and 80 per cent. As appeared indicated from time to time the experiment was terminated arbitrarily or allowed to continue until one or both of the dogs died. In a large number of experiments the respiration of the high oxygen concentration was continuous, but in others various degrees of interruption were tried.

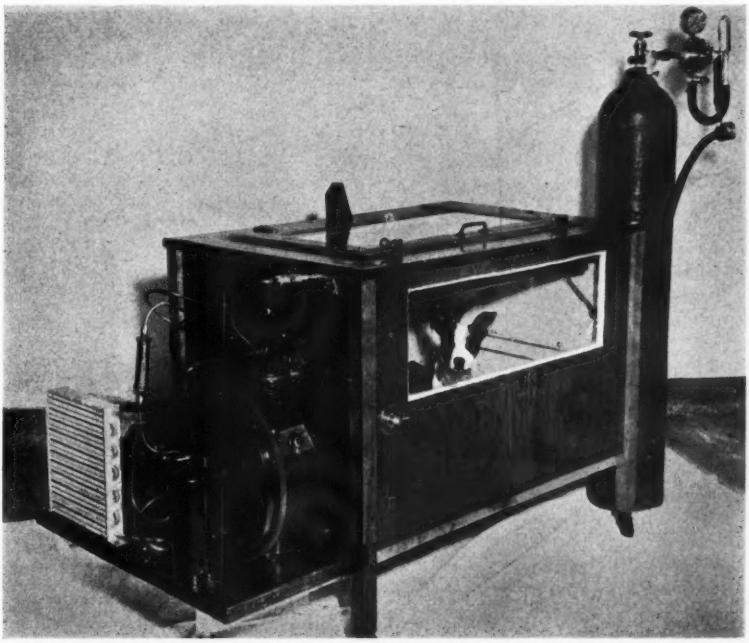


Fig. 1.—Oxygen chamber with attached refrigerating unit and flow meter.

In some instances the blood pressure of the animals was determined at the beginning and end of the experiment by inserting a needle connected to a mercury manometer into the femoral artery. Likewise, the venous pressure was determined by the insertion of a needle connected to a manometer filled with 2.5 per cent sodium citrate solution into one of the superficial veins of the lower leg. Venous blood was used to estimate the hemoglobin and R.B.C. before and after the experiments.

In a few animals the oxygen capacity and oxygen saturation of arterial blood were determined. Readings taken at the end of the experiment were obtained as soon as possible after the animal was removed from the oxygen chamber. During the short interval intervening, a mask was held tightly over the dog's nose and mouth and oxygen flushed through it at a rate of 15 liters per minute.

Animals were sacrificed by the intravenous injection of an overdose of sodium pentobarbital. Autopsies were performed on all animals immediately after death.

The lungs and heart together with the trachea were removed en masse and fixed in formalin. Later, sections of these were cut, embedded in paraffin, and sectioned for histologic study. All sections were stained with hematoxylin eosin. In some animals pleural effusions were noted at autopsy. The quantity of fluid present was measured, and a sample was analyzed.

ANALYTICAL METHODS

Control of the composition of the gas in the oxygen chamber was maintained by frequent analysis. Oxygen plus carbon dioxide was measured by absorption in alkaline pyrogallol with a simple apparatus of the Orsat type. Since the carbon dioxide content was kept below 2 per cent, the result of this analysis may be taken to represent the oxygen content for practical purposes. The carbon dioxide content was determined separately by absorption in potassium hydroxide. Less frequently both carbon dioxide and oxygen were determined by successive absorption in a precision Haldane apparatus.

The composition of the intestinal gas of the dogs with obstruction was determined on samples of 1 to 2 c.c. aspirated from the Biebl loops with an oiled syringe fitted with a stopcock and 20 gauge needle. The gas samples were transferred immediately to storage tubes by mercury displacement and were analyzed within twenty-four hours by means of a micro apparatus of the dry reagent type. All manipulations were made in a system completely enclosed with mercury. Oxygen was absorbed by solid yellow phosphorus, and carbon dioxide, by a freshly prepared solid bead of caustic soda. Accuracy was assured by analyses of outdoor air and of known gas mixtures.

Blood gas content and oxygen capacity were determined by the standard Van Slyke methods. Blood samples from the femoral artery were drawn under oil with immediate transfer to storage over mercury. Hemoglobin was also estimated as acid hematin in a photoelectric colorimeter.

Pleural fluid was analyzed for nitrogen by acid digestion and nesslerization, using a photoelectric colorimeter. The same method was used to estimate nonprotein nitrogen in blood plasma. Protein concentration in the blood plasma was calculated from the difference between total N and N.P.N. The factor 6.25 was used to convert nitrogen content into protein equivalent.

RESULTS

The results of the analysis of the intestinal gas in four dogs with complete obstruction in the terminal ileum when made to respire 95 to 100 per cent oxygen are given in Table I. Dog 3 died after 13.75 hours from peritonitis so that only two gas samples were obtained. Attempts to obtain gas samples from Dog 4 after seven hours were unsuccessful. Only fecal content could be aspirated. It is interesting to note that at post-mortem examination no gas could be found in the intestinal tract of either of these animals.

In Table II are recorded the results of the analyses for four dogs with complete obstruction of the sigmoid colon. A greater interval of time was allowed to elapse between the time of obstruction and the beginning of the experiment than those instances in which the terminal ileum was obstructed.

In general the results obtained in these two groups of animals were the same. The carbon dioxide concentration in the intestinal gas at

TABLE I

ANALYSIS OF INTESTINAL GAS OF DOGS WITH TERMINAL ILEAL OBSTRUCTION CONFINED IN AN ATMOSPHERE CONTAINING 95 TO 100 PER CENT OXYGEN

DOG	DURATION OF OBSTRUCTION BEFORE OXYGEN ADMINISTRATION (HOURS)	TIME AFTER BEGINNING OF OXYGEN ADMINISTRATION (HOURS)	ANALYSIS OF INTESTINAL GAS		TOTAL DURATION OF EXPERIMENT (HOURS)	CONTENTS OF OBSTRUCTED PORTION OF BOWEL AT END OF EXPERIMENT (C.C.)	
			PER CENT OXYGEN	PER CENT CARBON DIOXIDE		GAS	FLUID AND FECES
1	48	0.0	11.8	4.6	46.5	50	300
		7.0	4.1	8.6			
		13.0	21.1	0.4			
		24.0	29.1	6.3			
		30.5	19.9	1.7			
		36.0	18.4	2.7			
		46.5	9.2	11.0			
2	48	0.0	4.7	7.8	52.5	90	450
		4.5	8.5	6.4			
		10.5	12.4	6.3			
		28.5	19.1	2.6			
		34.5	20.2	1.1			
		52.5	7.8	11.2			
3	72	0.0	4.3	10.4	13.7	None	155
		6.5	18.8	4.3			
4	72	0.0	2.6	11.4	41.5	None	170
		7.0	22.7	6.7			

TABLE II

ANALYSIS OF INTESTINAL GAS OF DOGS WITH OBSTRUCTION OF SIGMOID COLON CONFINED IN AN ATMOSPHERE CONTAINING 95 TO 100 PER CENT OXYGEN

DOG	DURATION OF OBSTRUCTION BEFORE OXYGEN ADMINISTRATION (HOURS)	TIME AFTER BEGINNING OF OXYGEN ADMINISTRATION (HOURS)	ANALYSIS OF INTESTINAL GAS		TOTAL DURATION OF EXPERIMENT (HOURS)	CONTENTS OF OBSTRUCTED PORTION OF BOWEL AT END OF EXPERIMENT	
			PER CENT OXYGEN	PER CENT CARBON DIOXIDE		GAS	FLUID AND FECES
5	48	0.0	1.3	10.3	46.0	50	300
		6.5	19.8	1.3			
		11.5	19.9	1.2			
		24.0	18.4	1.7			
		30.0	16.4	1.6			
		35.5	7.7	25.6			
		46.0	17.5	36.2			
6	96	0.0	4.4	12.9	47.0	None	450
		8.0	15.9	6.1			
		22.0	13.1	16.4			
		32.0	12.7	22.5			
7	96	0.0		15.0	48.5	20	400
		21.0	17.5	16.6			
		33.5	12.7	3.7			
		48.5	24.3	10.0			
8	96	0.0	1.3	21.4	40.5	20	100
		4.5	0.6	7.3			
		9.0	14.3	4.0			
		18.0	13.9	3.8			
		26.0	16.3				
		33.0	17.0	2.3			
		39.5	17.7	3.1			

first decreased and then increased. The time interval after subjecting the dogs to a high oxygen concentration before this reversal of trend occurred was about twenty-four hours with ileal obstructions and thirty hours with colonic obstructions. The carbon dioxide concentration in the colon was greater than in the ileum. Conversely, the oxygen concentration was lower in the colon than in the ileum. These relationships are in keeping with Hibbard's results obtained on dogs with intestinal obstruction studied at this clinic in 1936.

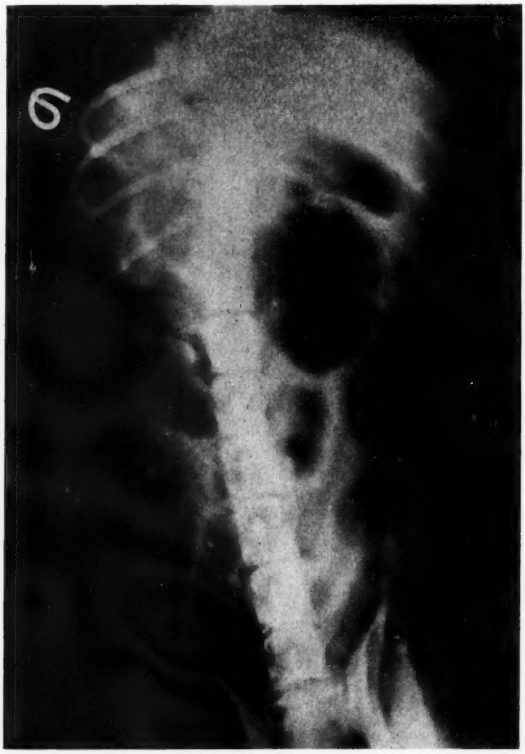


Fig. 2A.—Roentgenogram of Dog 4. Film of abdomen taken after seventy-two hours of obstruction before being confined to oxygen chamber. Quantities of gas can be seen in stomach and small bowel. (This animal had a complete obstruction of the terminal ileum before being confined in an atmosphere of 95 to 100 per cent oxygen for 41.5 hours.)

Gas analyses furnished no measure of the effectiveness of the respiration of a high oxygen concentration in removing accumulations of gas from the body, but x-ray films of the dogs so studied furnish convincing evidence on this point. In addition, the quantities of gas remaining in the intestinal tract, excluding the stomach, at the conclusion of the experiment have been recorded in Tables I and II. These measured amounts were consistently less than is found with the same type of

obstruction persisting for an equal period of time, namely, 250 c.c. with ileal obstruction and 300 c.c. with colonic obstruction (Hibbard). Figs. 2*A* and *B* illustrate the decrease in the quantity of gas in the intestinal tract of Dog 4 incident to the prolonged respiration of a high oxygen concentration.

The histologic examination of the lungs of some of the dogs dying during the course of the above experiments revealed a diffuse hyperemia of the pulmonary parenchyma and in some instance mild pulmonary edema. These findings brought up the question of oxygen poisoning as a possible cause of death.

Fig. 2*B*.—Roentgenogram of Dog 4. Film of abdomen taken after being confined in an atmosphere of 95 to 100 per cent oxygen for 41.5 hours. There is almost a complete absence of gas throughout the entire gastrointestinal tract. Other dogs show absence of gas in intestine, but a dilatation of the stomach with gas.

The remainder of the experiments here reported were performed to study the general effects of respiring high concentrations of oxygen by normal dogs. For this purpose a total of forty-nine dogs were employed. Forty-one animals were made to respire 95 to 100 per cent oxygen; six were made to respire 85 to 90 per cent oxygen; and two were made to respire 75 to 80 per cent oxygen. Some of the results

obtained have been included in Table III. The continuous respiration of oxygen in a concentration of 95 to 100 per cent causes death of the dog usually in about thirty-nine hours. There is, however, a marked individual variation in resistance. One dog died after six hours with typical pathologic findings, but another animal lived for ninety-four hours. A concentration of 85 to 90 per cent oxygen was tolerated much better. One dog died after seventy-two hours, but another animal confined in the box with this one, although definitely poisoned, survived when removed from the box at the end of seventy-two hours. Two other dogs confined in the box for 118 hours showed unmistakable symptoms of poisoning but did not die. One of these was sacrificed, and the other recovered. A concentration of oxygen of 75 to 80 per cent was withstood even better. Two dogs were confined in such an atmosphere for one week. Mild symptoms of poisoning were present at the end of this time when the experiment was discontinued. One of the animals was sacrificed, and the other was allowed to survive.

TABLE III

SURVIVAL PERIODS OF DOGS MADE TO RESPIRE HIGH CONCENTRATIONS OF OXYGEN

	AV. PERIOD
95-100 per cent Oxygen—41 dogs	
Continuous Administration—27 dogs	
10 animals *died* after 6 to 94 hr.	39 hr.
15 animals *sacrificed* after 1 to 48 hr.	
2 animals *survived* after 52 hr.	
Interrupted Administration—14 dogs	
a. 1 interruption of 45 min. after 24 hr.—6 dogs	
5 animals *died* after 42.5 to 64 hr.	55.5 hr.
1 animal *survived* after 57 hr.	
b. 1 interruption of 45 min. each day—4 dogs	
4 animals *died* after 42.5 to 167.5 hr.	117 hr.
c. 3 interruptions of 15 min. each every day—4 dogs	
2 animals *died* after 41 hr.	41 hr.
2 animals *sacrificed* after 168 hr.	
85-90 per cent Oxygen—6 dogs	
Continuous Administration—6 dogs	
1 animal *died* after 72 hr.	
1 animal *sacrificed* after 118 hr.	
2 animals *survived* after 72 and 118 hr.	
Interrupted Administration	
1 interruption of 45 min. after 24 hr.—2 dogs	
2 animals *sacrificed* after 105 hr.	
75-80 per cent Oxygen—2 dogs	
Continuous Administration—2 dogs	
1 animal *sacrificed* after 170 hr.	
1 animal *survived* after 170 hr.	

The effect of interrupting the respiration of a high oxygen concentration on the ability of dogs to survive was noted in sixteen experiments. In six instances the respiration of 95 to 100 per cent oxygen was interrupted once for approximately forty-five minutes during the second twenty-four-hour period of the experiment. Five of these animals died after periods varying from 42.5 to sixty-four hours. The

average survival time was 55.5 hours as contrasted to thirty-nine hours when no interruption occurred. In four instances, a forty-five-minute interruption was made each twenty-four hours. The average survival time of these dogs was 117 hours. Ninety-five to 100 per cent oxygen was administered to four dogs with a fifteen-minute interruption three times a day. Although two of these animals died after forty-one hours, two others lived 168 hours at which time they were sacrificed. It should be stated, however, that, during the experiment in which the dogs died after forty-one hours, the temperature in the oxygen chamber rose to over 90° F. over a considerable period of time. This was due to a failure of the refrigerating unit, and it is thought that this contributed to the rapid death of both animals. Campbell found that animals succumbed sooner to a higher temperature when confined in a high concentration of oxygen.

TABLE IV

LENGTH OF TIME FOR DEVELOPMENT OF DYSPNEA IN DOGS MADE TO RESPIRE HIGH CONCENTRATIONS OF OXYGEN

CONCENTRATION OF OXYGEN	NO. OF DOGS	TIME INTERVAL (HOURS)		
		MINIMUM	MAXIMUM	AV.
95-100% (continuous administration)	17	4	76	34.5
95-100% (one 45-min. interruption daily)	6	32	49	42.5
95-100% (three 15-min. interruptions daily)	2	29	67	48
85-90% (continuous administration)	6	32	79	47.5

The symptoms of poisoning as observed in animals respiring high concentrations of oxygen were unmistakable and followed a definite sequence in their appearance and progression. Within a few hours, the dogs became lethargic and appeared to sleep most of the time. After twelve to eighteen hours, food was refused, but water or milk would usually be taken until dyspnea appeared. Once developed, dyspnea usually continued with increasing severity until the animal died. In some instances the respiratory rate was decreased to 8 to 10 per minute. Expiration was definitely prolonged more than inspiration, and all the accessory muscles of respiration were brought into play. Extreme respiratory arrhythmia of the heart resulted from the abnormally elevated intrathoracic pressure during expiration. In some animals, long periods of lethargy would be broken by intervals of restlessness during which the animal coughed persistently and raised small amounts of white froth. Auscultation of the chest, when marked dyspnea was present, revealed weak high-pitched wheezes, such as are heard during acute attacks of asthma. Not infrequently no respiratory murmur could be detected at all.

The development of definite dyspnea was taken to indicate the presence of oxygen poisoning. In Table IV is recorded the time interval

after the beginning of the experiment and before this symptom was noted.

It was impossible to predict with any degree of certainty how long an animal would survive, after it became dyspneic. In some instances, death supervened within two or three hours; in others, the most intense dyspnea would continue for as long as forty-eight hours. Shortly before death, all animals became intensely cyanotic.

TABLE V

OBSERVATIONS ON BLOOD OXYGEN OF DOGS MADE TO RESPIRE HIGH CONCENTRATIONS OF OXYGEN

DOG	DURATION OF EXPERIMENT (HOURS)	CONCENTRATION OF OXYGEN IN RESPIRED AIR (%)	DEGREE OF PULMONARY PATHOLOGY PRESENT	TOTAL OXYGEN CAPACITY OF ARTERIAL BLOOD (VOLUMES PER CENT)		PER CENT SATURATION OF ARTERIAL BLOOD	
				BEFORE	AFTER	BEFORE	AFTER
18	105 (with 45-min. interruption)	85- 90	Moderate (sacrificed)	20.29	25.92	93.5	93.0
19	105 with 45-min. interruption)	85- 90	Moderate (sacrificed)	19.44	24.14	98.0	94.5
47	95 (with 45-min. interruption)	95-100	Marked (dog moribund)	24.06	27.68	96.0	62.3
48	95 (with 45-min. interruption daily)	95-100	Marked (survived 60 hr.)	23.27	18.86	93.0	83.0
39	24 (continuous administration)	95-100	Slight (sacrificed)	19.90	20.90	91.0	100.0
22	30 (continuous administration)	95-100	Marked (sacrificed)	17.76	21.88	91.0	99.0
23	30 (continuous administration)	95-100	Marked (sacrificed)	21.81	22.55	90.0	100.0
17	47 (continuous administration)	95-100	Moderate (sacrificed)	8.43	8.46	94.5	98.0
33	48 (continuous administration)	95-100	Slight (sacrificed)	20.55	20.03	93.5	100.0

In nine dogs, measurements were made of the oxygen capacity and saturation of the arterial blood before and after the development of oxygen poisoning. The results are tabulated in Table V. There was apparently a consistent, slight increase in the oxygen-carrying capacity of the blood, incident to the poisoning. Only one dog, Dog 48, did not show this. Dog 17 was obviously anemic. The oxygen saturation showed an increase in some instances, and a decrease in others (note Dog 47). The degree of saturation would appear to depend upon the severity of the pathologic changes in the lungs.

The blood pressure in the common femoral artery was measured in six dogs, before and after poisoning. In all six animals a slight increase was noted. In four animals the venous pressure was measured in one of the superficial veins of the hind legs. In two instances no change was de-

tected, but in the other two animals, an increase of over 100 per cent was noted.

In fifteen dogs the blood nonprotein nitrogen and blood proteins were measured before and after the development of oxygen poisoning. Little change was noted. The average nonprotein nitrogen before poisoning was 36.3 mg. per cent and afterward, 42.0 mg. per cent. Similarly the average level of the blood proteins before was 5.6 Gm. per cent and afterward, 5.8 Gm. per cent.

Twelve dogs dying of oxygen poisoning were found at autopsy to have pleural effusions varying in amount from 20 to 225 c.c. Samples of this fluid in each instance were analyzed to determine its protein content. This was found to vary from 3.7 Gm. per cent to 7.0 Gm. per cent. The average was 4.9 Gm. per cent.

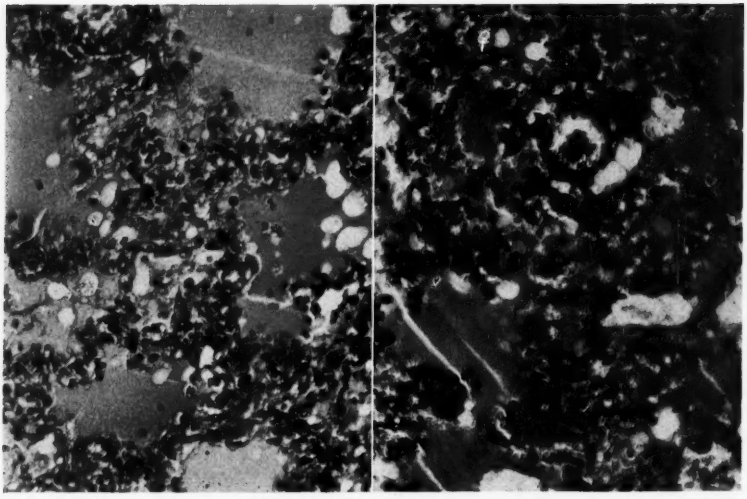
PATHOLOGIC FINDINGS

The gross pathologic findings for all dogs dying of oxygen poisoning were remarkably consistent. The muscles and abdominal viscera were cyanotic. The small intestine and colon were contracted and empty of gas. The stomach, on the other hand, was usually distended with gas. The kidneys appeared to be congested. The spleen was contracted and rubbery in consistency. The liver was bluish black and appeared to be of normal size. Mention has already been made of the frequent finding of pleural effusions. In other animals, although no fluid was present, strands of fibrin could be seen extending over the visceral pleura. All of the lungs exhibited signs of congestion. This congestion in places was so intense that the pulmonary parenchyma had the appearance and consistency of normal liver tissue. These areas of maximal congestion were most likely to be found for some unexplained reason in the lower lobes and on the dorsal surfaces of these lobes. The trachea and bronchial tree were frequently found filled with a white froth.

The microscopic findings in general showed hyperemia and congestion of the kidneys, liver, and lungs, with a contracted and relatively bloodless spleen. The sinusoids of the spleen were practically empty; all the blood was in the pulp. The sinusoids of the liver were packed with red blood cells, and, in some instances, a marked atrophy of the hepatic parenchyma in the central part of the lobules, such as is seen in right heart failure, was found.

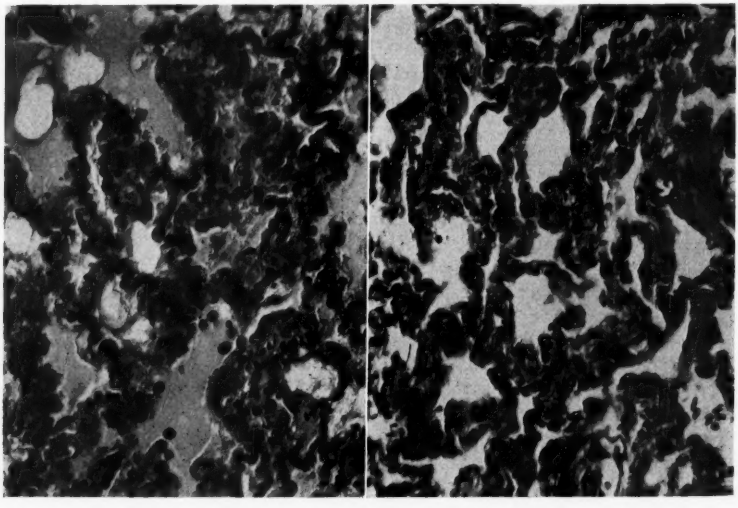
Sections taken from the lungs showed varying degrees of the same pathologic picture; namely, hyperemia, congestion of the alveolar capillaries, interstitial hemorrhage, and pulmonary edema. Large portions of certain lungs showed every alveolus completely filled with fluid. On the other hand, there was little extravasation of blood into the air spaces. There were also scattered areas of leucocytic infiltration. These leucocytes were largely polymorphonuclear.

The same changes, except in a lesser degree, were found in those animals with symptoms of poisoning that were sacrificed. Furthermore, definite lesions could be present without any clinical signs of poisoning. Some of the animals were sacrificed after very short exposures to determine how soon the above described findings appeared. Unmistakable changes in the lungs, consisting of hyperemia and congestion, were found after as short a period of time as two hours of exposure to 95 to 100 per cent oxygen. In those animals subjected to 75 to 80 per cent oxygen for a week and then sacrificed, changes similar to those described above were observed, but in a much less marked degree. Certain of those animals which became poisoned but survived were sacrificed two weeks to three months later. These animals appeared to be entirely normal to both gross and microscopic examination.



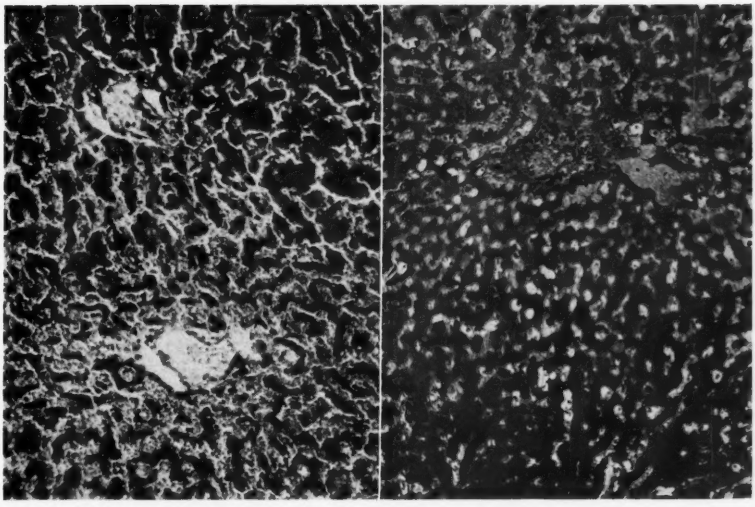
A. *B.*

Fig. 3.—*A* and *B*, Histologic sections of the lung of a dog confined in a atmosphere of 90 to 100 per cent oxygen and dying after fifty-seven hours. The respiration of the high oxygen concentration was interrupted once during this period for forty-five minutes. It can be noted that the capillaries in the alveolar walls are distended with blood and that the alveolar spaces are filled with exudate.

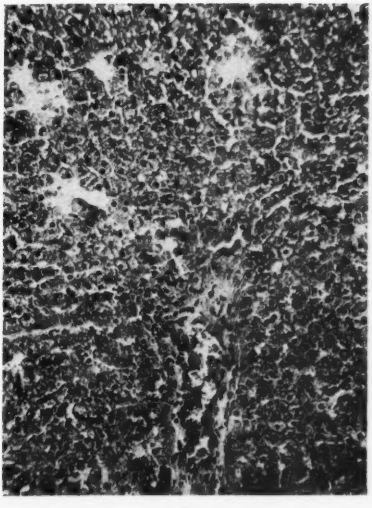


A. *B.*

Fig. 4.—Histologic sections of the lungs of dogs confined in an atmosphere containing 75 to 90 per cent oxygen. *A*, Histologic section of the lung of a dog confined in an atmosphere of 85 to 90 per cent oxygen for ninety-one hours. The respiration of the high oxygen concentration was interrupted once during this period for forty-five minutes. The pathologic changes in this section are practically identical with those seen in Fig. 3. *B*, Histologic section of the lung of a dog confined in an atmosphere of 75 to 90 per cent oxygen for 168 hours. There was no interruption of the respiration of this concentration of oxygen. This animal was sacrificed, and at this time there were only moderate symptoms of oxygen poisoning. Similar but less marked pathologic changes are present.

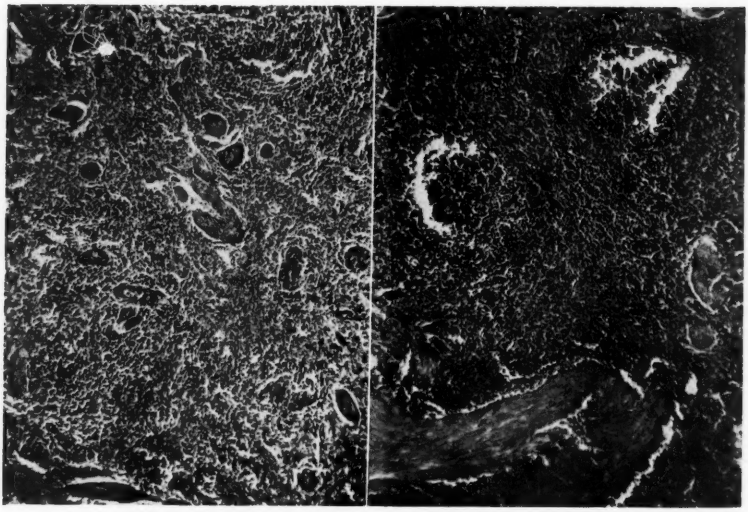


A. *B.*

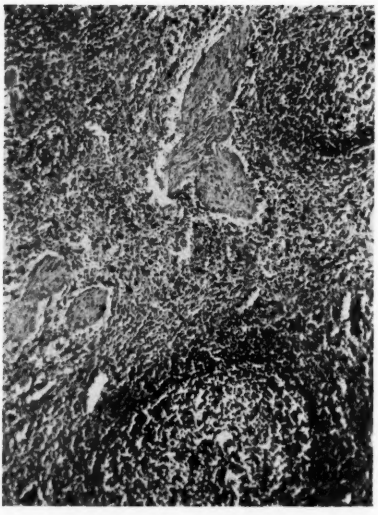


C.

Fig. 5.—Histologic sections of the liver of dogs confined in an atmosphere containing a high concentration of oxygen. *A*, Histologic section of the liver of the same dog as in Fig. 3. Atrophy of the parenchymal cells in the vicinity of the central vein is very evident. *B*, Histologic section of the liver of the same dog as in Fig. 4*A*. The degeneration of the parenchymal cells about the central vein, while definite, is less marked than that seen in Fig. 5*A*. *C*, Histologic section of the liver of the same dog as in Fig. 4*B*. There is very little change of the parenchymal cells.



A. *B.*



C.

Fig. 6.—Histologic sections of the spleen of dogs confined in an atmosphere containing a high concentration of oxygen. *A*, Histologic section of the spleen of the same dog as in Fig. 3. *B*, Histologic section of the spleen of the same dog as in Fig. 4*A*. *C*, Histologic section of the spleen of the same dog as in Fig. 4*B*.

DISCUSSION

These experiments show without question that the prolonged respiration of an atmosphere containing over 75 per cent oxygen causes deleterious effects in the dog, which, if severe enough, cause death. The finer and precise physiologic mechanism by which these changes are produced has been a subject of considerable debate and is not understood fully. As far back as 1913, Retzlaff[14] concluded that a vasoconstriction of the pulmonary vessels might be responsible for the sequence of events in oxygen poisoning. In 1930, Wolff and Lennox[16] made direct observations on the pial arterioles of cats, and in 1931, Cobb and Fremont-Smith[10] studied the vessels of the human retina and concluded that high concentrations of oxygen produced a vasoconstriction. Cusick, Benson, and Boothby[11] in 1940, likewise observed arteriolar constriction in the retinas of patients inhaling extremely high concentrations of oxygen. These observations furnish clues which might well be investigated with profit. It is not impossible that most or all of the pathologic changes, which we have observed, might be explained by an hypothesis of deranged vascular physiology. This may well account for the presence of the fluid, the composition of which is similar to that of serum, in the alveoli. To be sure, the irritated respiratory epithelium is a direct effect and must limit the diffusion of the respiratory gases.

The contraction of the spleen found at autopsy in dogs dying of oxygen poisoning is most probably a manifestation of asphyxia. The passive congestion of the liver and other abdominal viscera can be explained easily by assuming an increase in the resistance to the pulmonary blood flow. The changes in the composition of intestinal gas, which have been described, are also best explained by the apparent interference with normal exchange of oxygen and carbon dioxide between the blood and alveolar air. Whether a stasis of blood in the portal system secondary to increased resistance to pulmonary blood flow also plays a part is not known. Such an effect is possible.

Our knowledge concerning the toxic effects of high oxygen concentrations on human beings is meager indeed. Becker-Freyseng and Clamann subjected themselves to a concentration of oxygen of 90 per cent for sixty-five hours. The symptoms which they experienced would indicate that certain pulmonary changes occurred which might lead to serious consequences. The experiments here related show that the general effects of oxygen poisoning in the dog are similar to those occurring in small laboratory animals. There is no reason to suppose that the effects in man would not be similar. Evidence is thus furnished which confirms the practice of limiting the period of time during which patients may be safely treated by the administration of a high concentration of oxygen.

Furthermore, it has been pointed out that several adequate interruptions of the inhalation of high-oxygen mixtures during the course of

exposure undoubtedly delay the deleterious effects of oxygen. In this connection, it may be well to reiterate that pathologic changes occur before signs and symptoms manifest themselves. This, no doubt, explains the lack of detecting oxygen poisoning clinically, despite the frequent use of high percentages of oxygen.

Though on numerous occasions in the past the age of the animal was described as being a factor in the length of time of survival to high oxygen exposures, we cannot concur with this opinion. Three puppies, 3 weeks of age, were studied and found to be equally as susceptible as adults.

SUMMARY

Four dogs with complete obstruction of the terminal ileum of forty-eight to seventy-two hours' duration were confined in an atmosphere of 95 to 100 per cent oxygen for periods of time up to 52.5 hours. The oxygen content of the intestinal gas in these dogs rose from an average initial value of 5.8 per cent to about 22 per cent at twenty-five hours and then decreased. Conversely, the carbon dioxide concentration decreased from about 15 per cent to about 2 per cent within twenty-five hours and then gradually increased. Four other dogs with complete obstruction of the sigmoid colon of forty-eight to ninety-six hours' duration were confined in 95 to 100 per cent oxygen for periods of time up to 48.5 hours. Changes in the composition of the gas in the colon similar to those found in dogs with obstruction in the terminal ileum were observed. The concentration of oxygen was lower and the concentration of carbon dioxide was higher, however. The total amount of gas in the obstructed portion of the intestinal tract was noted to be greatly decreased by the respiration of the high oxygen concentration. The stomach on the other hand usually was found to be dilated.

The general effects of respiring concentrations of oxygen in air above 75 per cent for prolonged periods of time were studied in forty-nine dogs. Pathologic changes consisting of hyperemia and congestion were found to be uniformly present in the kidneys, liver, and lungs. The lungs in addition exhibited a marked amount of pulmonary edema, particularly in those dogs which died of the poisoning. The intestinal tract was empty of gas, but the stomach was usually distended with gas. The severity of symptoms, the degree of pathologic change, and the susceptibility of the animal to the poisonous effects varied directly with the concentration of oxygen and the time of exposure. A great individual variation in the ability of dogs to withstand exposure to a high concentration of oxygen was noted. Definite changes in the lungs were seen after two hours' exposure to 95 to 100 per cent oxygen. With 95 to 100 per cent oxygen, death occurred on the average at thirty-nine hours. Interruption of the administration of high concentrations of oxygen definitely increased the ability of the dog to withstand the toxic

effects. The symptoms of oxygen poisoning were noted to be, in the order of their appearance, (1) lethargy, (2) anorexia, (3) dyspnea. The oxygen capacity of dogs poisoned by the respiration of a high oxygen concentration was consistently increased. No consistent change in the oxygen saturation of the blood of these same dogs was observed. Many dogs dying of oxygen poisoning were found at autopsy to have a pleural effusion. This fluid had a protein content approaching that of blood plasma.

CONCLUSIONS

1. The respiration of 95 to 100 per cent oxygen by dogs with intestinal obstruction increases the concentration of oxygen and decreases the concentration of carbon dioxide in the intestinal gas for twenty-four to thirty-six hours. After this time, the concentration of oxygen decreases and the concentration of carbon dioxide increases.

2. The prolonged respiration of a concentration of oxygen over 75 per cent by dogs produces pathologic changes in the organs studied, namely, lungs, liver, spleen and kidneys. The cause of these changes is not known. The spleen is contracted. The lungs, liver, and kidney are congested and hyperemic.

3. The continuous administration of an atmosphere containing 95 to 100 per cent oxygen and 0.2 to 2 per cent carbon dioxide at a temperature of 70 to 80° F. causes death in dogs on the average at thirty-nine hours. There is a wide individual variation, however, in the resistance of dogs to the lethal effects of extremely high concentration of oxygen.

4. The continuous respiration of an atmosphere containing 75 to 90 per cent oxygen produces pathologic changes similar to those seen with 95 to 100 per cent. The time required for these changes to appear, however, is considerably longer.

5. The interruption of the administration of a concentration of oxygen capable of producing pathologic changes increases the time necessary for these changes to develop.

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DISCUSSION

DR. JOSEPH TANNENBERG, New York, N. Y.—Some fifteen years ago, I made a few observations which might perhaps help to explain the mechanism of oxygen poisoning. In these experiments, the aim was observation of the pulmonary circulation in the living animal under the microscope while various drugs were administered.

These experiments were made on the frog. When the exposed lung was rinsed with saline saturated with oxygen, it could be seen that the small pulmonary arteries and arterioles became constricted and remained so during the application of the oxygen-saline. This constriction immediately changed as soon as the oxygen-saline was changed to simple saline, or to saline that was saturated with carbon dioxide.

It appears to me that generalized constriction of the pulmonary arteries and arterioles, produced by excessive oxygen partial pressure, might be a great strain on the heart. If maintained for some time, this might account for failure of the circulation as manifested by passive congestion in the liver and in the lung, producing engorgement of the pulmonary capillaries and pulmonary edema as reported in the experiments of Dr. Paine.

DR. JOHN R. PAINE.—I wish to thank Dr. Tannenberg for this discussion.

There is evidence from Dr. Lennox, in Boston, and Dr. Cusick, in the Mayo Clinic, that respiration of high-oxygen concentrations produces restriction of arterioles. Dr. Lennox has observed this in the pial blood vessels, and Dr. Cusick, in the retinal blood vessels. How these changes came about, I do not know, but they are very interesting. It is one of the problems with which we are working at the present time.

If I can persuade our Department of Physiology to prepare a certain number of heart-lung preparations for our use, we will subject these lungs to high concentration of oxygen; it may be possible to rule out or rule in the nervous factor in control of the blood vessels, if we can show, as we believe we can in the intact animal, changes within two hours. That is what we have in mind.

CHRONIC NONTUBERCULOUS EMPYEMA

ALBERT O. SINGLETON, M.D., AND ROBERT M. MOORE, M.D.
GALVESTON, TEXAS

IN NO region of the body has surgery advanced more rapidly during recent years than in the thorax. But chronic empyema, one of the oldest surgical diseases of the chest, is still poorly handled, and in most localities it remains the "patriarch of the surgical scrap heap." The treatment of acute empyema has improved with a progressive lowering of mortality since the World War days. Furthermore, now that the sulfonamide drugs are available, fewer cases of post-pneumonic empyema occur. In spite of these advances chronic empyema cases are still too numerous and continue to be a serious and difficult problem. About all general hospitals these unfortunate patients are found, with their deformed chests, clubbed fingers, and daily dressings. They may not be acutely ill, but they are completely incapacitated. In some the empyema has been present for one or two years while in others it has lasted for twenty years or more. Most of them have had many operations. The surgeon avoids them, and they continue the object of procrastination and neglect.

In our particular clinic we have had the responsibility for a number of these cases which have been sent to the University Hospital from distant rural communities. Some of these patients had had surgical drainage, usually of an inadequate type. Others had drained *per necessitatem*. Still others had been relieved by the development of a bronchial fistula with copious expectoration of pus. They are septic, anemic, and underdeveloped. The chest is deformed, and not infrequently there is marked curvature of the spine. To say that these unfortunates present a serious problem is to express it mildly.

We regret that after a long and fairly extensive experience with chronic empyema which was coupled with a careful attention to the literature upon the subject we are not able to add anything new to the knowledge of this disease. A critical study of thirty-three cases of chronic empyema is the subject of this paper. This seems to be a small number until one considers the work and worry and repeated operations which one case represents. Then a series of this size seems equivalent to several hundred ordinary surgical cases.

From the Department of Surgery, University of Texas, and John Sealy Hospital.
Read before the Twenty-Fourth Annual Meeting of the American Association for Thoracic Surgery, Toronto, Canada, June 9, 10, and 11, 1941.

CAUSE OF CHRONIC EMPYEMA

It is ordinarily stated that chronic empyema is the result of (1) inadequate drainage, (2) presence of foreign bodies, or (3) communications with the lung. In our own series the cause of chronicity was obvious in almost every instance. As soon as one inquired into the treatment of the original acute empyema, the persistence of the disease was explained. In many cases the presence of pus in the pleural cavity had not been recognized until a spontaneous sinus or a bronchial fistula occurred. Moreover, in other cases in which the original acute infection had been diagnosed the story was equally pitiful; a drain had been inserted and *left out after a few days to a few weeks.*

TABLE I

RESULTS WITH CLOSED DRAINAGE OF 172 CASES OF ACUTE EMPYEMA (115 MALES, 57 FEMALE)

(Of the 158 cases which recovered, only 6 (3.5%) became chronic.)

AGE GROUP	TOTAL	RECOVERED	DIED	MORTALITY %
Under 5 yr.	28	26	2	7.1
5 to 20 yr.	57	56	1	1.7
20 to 40 yr.	50	48	2	4.0
Over 40 yr.	37	28	9*	24.3
Totals	172	158	14	8.1

*Five over 60 years of age.

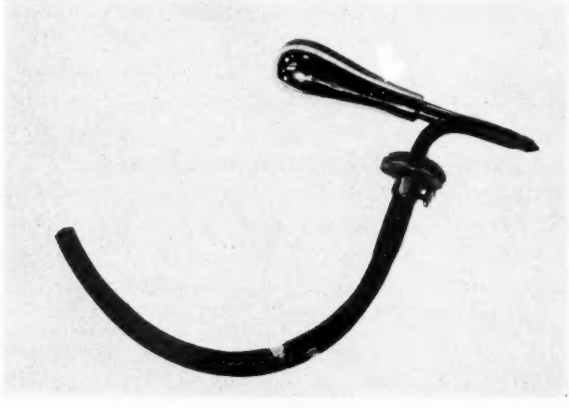

Fig. 1.—Empyema trochar and cannula.

That efficient and continued drainage is the greatest single measure in avoiding chronicity in empyema is shown by all reports of large series of cases. Table I summarizes the 172 consecutive cases of acute empyema treated by us. Of this series, only six cases persisted over a sufficient period of time to be classed as chronic empyema or to require further operative treatment. These 172 acute cases were treated by

intercostal drainage with a metal tube without rib resection, the drainage being of a "closed" type during the first seven to twelve days. While the mortality was unusually low and the number of chronic empyemas resulting was small, we do not claim that equally good results may not be obtained by rib resection and open drainage. In fact, Graham, Mason, and a score of others much prefer rib resection. Moreover, Weinberg[27] reported fifty-three consecutive cases of empyema treated by open intercostal drainage without a death and with low morbidity.

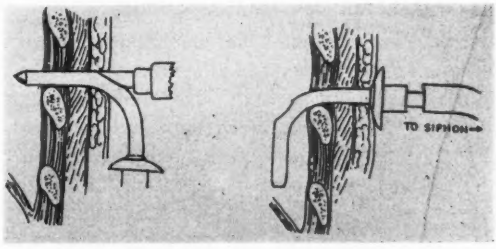

Fig. 2.—Trochar and cannula in place.

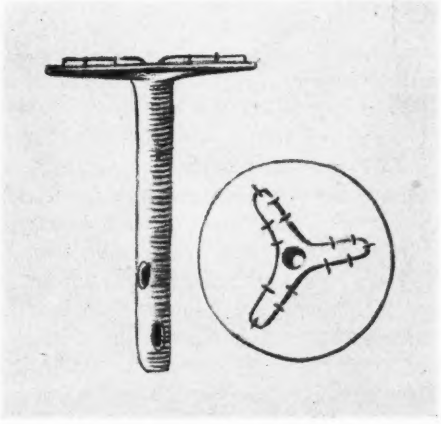

Fig. 3.—Rubber tube used after metal cannula was removed.

Constant, vigilant attention to see that uninterrupted drainage is secured is of much more importance than is the method of drainage. Even in protracted cases of empyema which have persisted for many months the establishment of adequate drainage may still result in proper cure. Furthermore, in patients who are quite septic and debilitated a marked improvement in health results from establishing good drainage, and this constitutes the first step in preparing the patient for a more serious operation which may be necessary to complete the cure.

An empyema cavity will not become obliterated as long as a foreign body is present. Similarly, while a bronchial fistula remains patent one cannot expect a cure. It is a common observation, however, that many of the smaller pleuropulmonary fistulas associated with acute empyema heal spontaneously in a short time. We have recently treated a child having a fistula which persisted for twenty-three months and then closed spontaneously without any treatment other than maintenance of the patency of the original drainage sinus (Case 25). On the other hand the closure of the fistula may defy one's extreme efforts.

TREATMENT OF CHRONIC EMPYEMA

Nonoperative measures which have been recommended in the treatment of chronic empyema include (1) vaccine therapy, (2) Beck's paste, and (3) high-vacuum suction. The first two methods fell into disrepute long ago. Noting the many successes reported in the older literature with the use of Beck's paste, one wonders why it has not remained a favorite remedy. Gurd[11] reported, "In general it may be stated that our experience in the use of Beck's paste has been extremely satisfactory." In 1909, Ochsner[17] enthusiastically recommended it. Now it is remembered only by the older surgeons. A number of years ago we tried the paste without success.

High-vacuum suction is a recent method reported to have resulted in cures in isolated cases.[15] We gave this method a thorough trial in three patients without improvement. In long-standing cases with thick-walled cavities it seems improbable that suction can have much influence. Moreover, in our experience troublesome hemorrhage from the granulations occurred when the negative pressure was great.

Of the *operative methods* used in treating chronic empyema the simplest is drainage. Almost every case of chronic empyema when first seen is draining inadequately. The introduction of a drainage tube of sufficient caliber is usually required. In a number of instances the establishment and maintenance of free drainage have sufficed to bring about a cure although at the beginning the cavity was large and seemed to be thick-walled (Cases 3, 8, 14, and 27). While in most instances a more formidable operative procedure is necessary, preliminary provision of satisfactory drainage can always be trusted to accomplish two desirable effects. It will lead to a diminution in the size of the cavity, and, at the same time, by preventing any accumulation of pus, it will relieve sepsis. Thus, in cases where drainage alone cannot accomplish a cure, it is a valuable preliminary measure to prepare the patient for serious operative procedures. For example, Case 27, an adult male, gained 58 pounds in ten weeks following the establishment of good drainage.

The surgeon who treats chronic empyema should be familiar with the various operative procedures which have been devised. The following are the most important operations.

1. Wilm's operation[28] consists of the resection of half-inch segments of several ribs at their angles posteriorly and at their costochondral junctions in front. A moderate amount of slumping of the wall over the cavity may result, but it is not sufficient ordinarily to obliterate the cavity.

2. Thoracoplasty, i.e., rib resection, was early employed to obliterate the dead space between the retracted lung and the chest wall. Estlander's operation consists of subperiosteal resection of three or four ribs with the object of making the external wall of the cavity more elastic so that it will collapse the cavity. We have practiced this procedure successfully in a number of cases.

3. Estlander and Schede modified this operation to include under the Schede operation the removal of ribs from the second to the tenth, together with the intercostal muscle aponeurosis and the parietal pleura and scar. A long U-shaped flap is lifted, carrying up with it the scapula and attached muscles. A visceral pleura is then thoroughly curetted, and the musculocutaneous flap is sutured in contact with the contracted lung. This extensive operation is accompanied by great shock, and this must be borne in mind.

4. In an effort to eliminate the deformity following extensive thoracoplasty Fowler,[6] and Delorme[4] devised the operation which bears their names. It provides a decortication of the lung by stripping away the firm, fibrous envelope from the surface of the retracted lung, allowing the lung to expand. Because of the extensive hemorrhage encountered and the difficulty in the dissection in some cases, Ransohoff (1914) made use of discission, i.e., the making of criss-cross incisions through the sclerosed visceral pleura, with satisfactory results. Decortication has had many advocates in the past. Gurd[11] reported marked success with this operation. In some cases, chiefly those which have not existed too long, decortication is easily accomplished and the immediate expansion of the lung to fill the cavity is very gratifying. In two children with fairly long-standing cavities we succeeded in estabishing a cure by decortication with very little difficulty and arrived at the conclusion that this was the operation of choice. Later, however, our experience has been that decortication may involve great loss of blood and serious wounding of the lung. One of our few operative deaths followed this procedure, the child succumbing to shock a few hours after operation in spite of transfusion and other efforts to combat shock (Case 20). Advocates of the operation have emphasized the importance of removing the parietal pleural as well as the visceral layer, but this step increases further the danger from hemorrhage. Our present attitude toward this operation is somewhat unfavorable.

Many efforts have been made to avoid the deformity which follows chronic empyema and the operations for its cure. Particularly in growing children one wishes to avoid deforming operations. Of the operations described, the thoracoplasties would seem at first glance to be the most deforming. However, in long-standing empyema a collapse of the chest has already occurred on the affected side. This is often accompanied by a scoliosis which has its concavity directed toward this side.[12, 22] Binnie,[2] remarked upon how little deformity persists after operations upon the thoracic cage and quoted Gluck, who stated, "It is not the removal of the chest wall but shrinking of its contents which is to blame." Recently Selig and Arnheim[22] have noted that the scoliosis which follows thoracoplasty is in the opposite direction to that following chronic empyema, i.e., its convexity is toward the operated side.

In many of the cases in our series the empyema was of such long duration (four to twelve years) that the chest was already hopelessly deformed and it did not seem that further deformity as a result of thoracoplasty was likely to be serious. Experience has borne out this

Fig. 4.

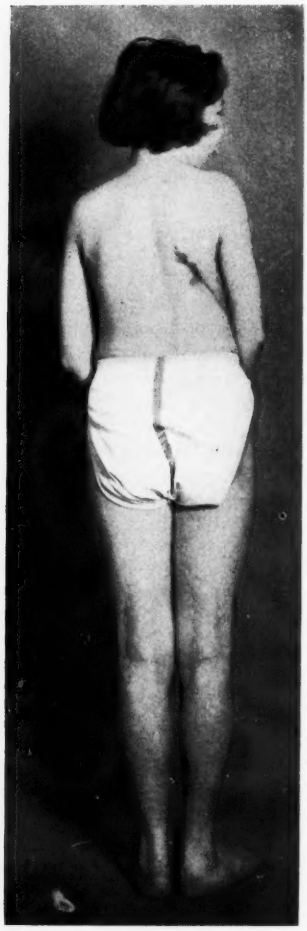

Fig. 5.

Fig. 4.—Marked lateral curvature resulting from chronic empyema. (Not a common occurrence.)

Fig. 5.—Chronic empyema of seven years' duration without lateral curvature.

opinion, and multiple-stage rib resection, because of its safety and because of the success we have obtained with it, has become our chief procedure in chronic empyema. After each stage the periosteal beds of

the resected ribs are treated with formalin. It is necessary to locate the cavity accurately so as to remove the proper ribs. Moreover, a sufficient number of ribs and a sufficient length of each rib must be removed. The total resection should extend one segment above the cavity and one segment below. When the cavity extends beneath the posterior angles of the ribs, the posterior ends of the ribs should be removed completely. In our experience this procedure has been particularly effective in chronic empyema in children (Cases 23, 24, and 31). Using it, one avoids much of the hemorrhage and shock which so often attend widespread excision of thickened pleural layers.

Fig. 6.—Skin incision for skin flap operation.

Wangensteen[26] has described the resection of ribs through short skin incisions. This procedure has merit and should be used wherever possible. In old cases, however, with the ribs rotated and approximated in a shingled position, larger skin incisions are required for exposure. The same is true in patients in which previous rib resection has led to irregular regeneration of bone. Moreover, it is well to remember that in both of these groups of cases the resection of ribs is accompanied by considerable loss of blood and is conducive to shock. For this reason multiple short operations are much to be desired. In one child, Case 20, we failed to observe this precaution and death occurred from operative shock in spite of everything we could do. In Case 21, a 14-year-old child with an empyema of eight years' standing, multiple rib resection failed to obliterate the cavity, and it finally became necessary to throw a sliding flap of skin and muscle into the cavity and to skin graft that part of the chest wall from which the flap was drawn.

Adults with long-standing cavities present added difficulties, especially when the cavities are large and one wall is formed by the mediastinum or pericardium. In these cases various modifications of the Schede-Estlander or Fowler-Delorme operation have been used. Muscle implantation is one of the most popular methods. Usually the latissimus dorsi is the muscle used, and an effort is made to preserve

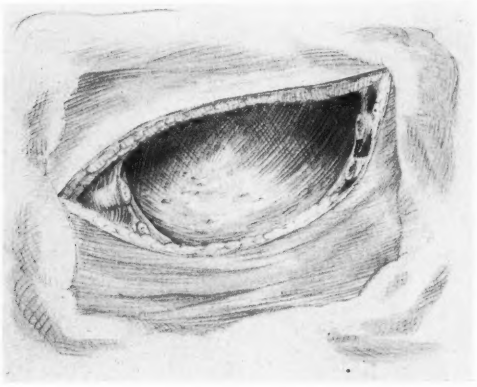

Fig. 7.—Roof of cavity removed.

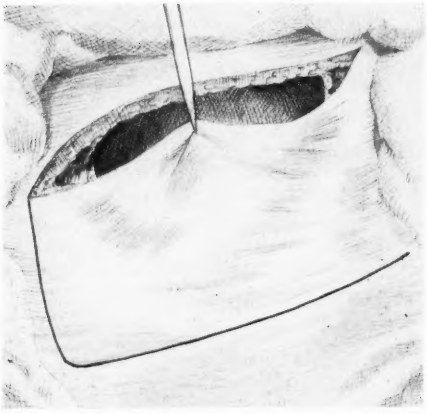

Fig. 8.—Large skin flap thrown up, hinged posteriorly.

its nerve and blood supply. Muscle flaps for plugging bronchial fistulas are often reported successful. Though success may follow this method, it is not unknown for the muscle to atrophy until it no longer fills the cavity or succumbs to infection and fibrosis. Carter[3] gave an excellent description of the method of utilizing muscle flaps in closure of chronic empyema cavities while others advocating muscle flaps include Robinson,[19] Kanavel,[13] Graham,[10] Stenbuck,[24] Wangensteen,[25] Garlock,[7] and

many others. In extremely difficult cases where more conservative measures have failed we have succeeded in some instances by unroofing the cavity, saucerizing it as much as possible, and sliding into the cavity a long musculocutaneous flap which was sutured to the deepest portion of the cavity, the more shallow portions of the cavity being left uncovered to epithelialize. Two such skin flaps may be necessary. The area of the chest wall from which a flap has been taken can be covered with a free skin graft.

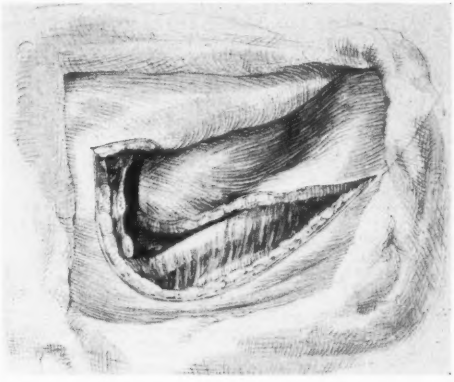

Fig. 9.—Skin flap stitched to bed of cavity. Area below cavity to be skin grafted.

Fig. 10.—Extensive cavity lined with large skin flap. Chest wall from which skin removed has been skin grafted.

Free transplants of fat have been used with success by Neuhoff in some extreme cases.[16] We have not made use of this method.

Clinical summaries of our thirty-three cases of chronic empyema appear at the end of the paper. Table II shows our results with the various operative procedures. Five deaths occurred in addition to a suicide (Case 1). Two patients (Cases 2 and 9) died of cardiac complications, these patients being 48 and 63 years of age. One death from operative shock has already been mentioned (Case 20). Moreover, two small children (Cases 15 and 29) entered in extremis from prolonged sepsis and died before anything more complicated than introduction of better drainage tube could be done. One boy who was cured of the empyema (Case 24) is known to suffer from some degree of amyloidosis as a result of prolonged sepsis. Case 16 is a somewhat unusual instance of a spontaneous cure.

TABLE II

RESULTS IN RELATION TO TREATMENT IN 33 CASES OF CHRONIC EMPYEMA

METHOD OF TREATMENT	CURED	DIED	STILL DRAINING
Drainage only	7	2	1
Removal of foreign body and drainage	2	0	0
Multiple stage rib resection	9	1	1*
Rib resection with musculocutaneous flap	3	1	0
Decortication	2	1	2 (1*)
Lobectomy and rib resection	1	0	0
Total	23	6†	4 (2*)

*Apparently cured but time too short to prove cure.
†One died by suicide.

SUMMARY

Thirty-three cases of chronic nontuberculous empyema are reported. In a number of instances the infection had remained present over a period varying from three to twelve years. It was apparent that the most important factor contributing to chronicity in these patients was inadequate surgical treatment during the primary acute stage. In this regard the treatment of acute empyema is mentioned briefly along with a report of the experience in treating 172 acute cases by intercostal closed drainage, six of which became chronic (Table I).

With respect to treatment of chronic empyema the experience with various operative procedures is discussed (Table II). The importance first of all of establishing a regime of adequate drainage is emphasized. In a number of cases this alone accomplished cure. Extensive one-stage operative procedures involving the wide opening of large cavities and decortication were found in some instances to lead to dangerous hemorrhage and shock. Multiple-stage rib resection is offered as a safe method for effecting cure in many cases, especially in long-standing empyemas in children.

CLINICAL SUMMARY OF CASES OF CHRONIC NONTUBERCULOUS EMPYEMA TREATED IN THE DEPARTMENT OF SURGERY, JOHN SEALY HOSPITAL, UNIVERSITY OF TEXAS

CASE 1.—A white male, aged 34 years, was admitted in 1916. Empyema was discovered by aspiration in January, 1916; glycerine and formalin were injected into

the cavity with apparent improvement. In August, 1916, a sinus developed at the aspiration site. In October, 1916, following preliminary drainage, a rib resection and decortication were done. The cavity continued to drain and was injected with Beck's paste in July, 1918. A musculocutaneous flap was thrown into the cavity in October, 1918. The patient committed suicide one month later before the result could be determined.

CASE 2.—A white male, aged 48 years, was admitted in January, 1918. The empyema had remained following pneumonia 3.5 months before admission. Drains were inserted. The patient died elsewhere in February, 1919, with the cavity still draining; death was reported as due to heart failure.

CASE 3.—A colored male, aged 21 years, was admitted in 1919. A spontaneous sinus had appeared on the chest eight months prior to entry. Drains were inserted. During the course of the treatment a drainage tube was lost in the chest and recovered by cystoscope two days later. Permanent cure resulted from drainage alone.

CASE 4.—A white male, aged 21 years, was admitted in 1919. A draining sinus had appeared on the chest fourteen months prior to entry. A drain was inserted. The patient left the hospital before the sinus was closed, and the ultimate outcome is unknown.

CASE 5.—A white male, aged 30 years, was admitted in 1919 and was cured by one operation which combined open thoracoplasty and muscle flap.

CASE 6.—A white male, aged 14 years, was admitted in 1920. An empyema had been drained in another city one year before, but a draining sinus persisted. X-ray examination revealed a drainage tube within the chest, and, after this was removed by cystoscope, permanent cure resulted.

CASE 7.—A white female, aged 25 years, was admitted in 1922. A chronic empyema had been present for four years prior to entry. An open thoracoplasty, followed later by a minor dissection of the external sinus, resulted in permanent cure.

CASE 8.—A white male, aged 40 years, was admitted in 1923. Five months prior to entry the aspiration of pus by the family physician had led to establishment of a draining sinus. Adequate open drainage led to cure.

CASE 9.—A white male, aged 63 years, was admitted with pneumonia in 1929. A closed drainage in March was followed by open thoracoplasties in September, November, and February, 1930. The patient died two days following the last operation, and autopsy established the occurrence of coronary occlusion.

CASE 10.—A white female, aged 6 years, was admitted with pneumonia in 1930. A closed drainage in February followed by open thoracoplasty in October resulted in cure. The patient died of pneumonia eight years later.

CASE 11.—A white female, aged 10 years, was admitted in 1931. Chronic empyema had been present for five years. Drainage tubes were inserted, but the patient was removed from the hospital and the outcome is not known.

CASE 12.—A white male, aged 21 years, was admitted with pneumonia in 1931. Closed drainage was followed by a persistent bronchial fistula. An open thoracoplasty two years and eight months later resulted in cure. The patient died of lobar pneumonia in 1936, and autopsy showed that the pleural cavity was clean.

CASE 13.—A colored male, aged 21 years, was admitted in 1932. Empyema followed a stab wound of the chest, and a draining sinus had been present for eight

months. A drain was inserted, and later an open thoracoplasty was done on two occasions. The patient refused continued treatment and left the hospital when the sinus was still draining. The outcome is not known.

CASE 14.—A white male, aged 28 years, was admitted in 1933. Empyema with bronchial fistula had been present for four months prior to entry. Establishment of better drainage resulted in cure. The patient died of an unrelated malignancy two years later.

CASE 15.—A white male, aged 10 years, was admitted in 1935 in extremis. A spontaneous sinus had appeared upon the chest twelve months before. A drain was inserted, but the patient died two days after admission. Autopsy showed the lung to be gangrenous.

CASE 16.—A colored male, aged 17 years, entered with pneumonia in July, 1935. Empyema followed. This patient was mentally defective and would not tolerate the slightest pain. The empyema was drained, but the patient ran away from the hospital repeatedly and would not submit to dressings. A bronchial fistula developed and could not be given proper care. A rib resection was done eight months following the drainage, but a few weeks later the patient ran away and disappeared for fifteen months. He returned at the end of that time completely cured. One year later he was a penitentiary inmate, but the empyema had not recurred. This was a striking example of natural cure. The patient had a large, open cavity with bronchial fistula which became completely healed in fifteen months with family care.

CASE 17.—A white male, aged 14 years, was admitted in 1936. An empyema had been drained elsewhere twelve months before but had persisted with bronchial fistula. Rib resection combined with decortication in November was followed by additional rib resection in January. The patient was discharged, cured, in April.

CASE 18.—A white male, aged 7 years, was admitted in 1936. Chronic empyema had been present for one year. Open thoracoplasty resulted in cure within two months.

CASE 19.—A white female, aged 23 years, was admitted with post-partum eclamptic convulsions in November, 1936. Acute nephritis with uremia, jugular thrombosis, pneumonia, and empyema followed. Because of the patient's critical condition the empyema was treated by daily aspiration until drowning almost occurred as a result of sudden bronchial fistula. A closed drainage was done at the bedside. The patient recovered, but a chronic cavity and sinus persisted. A decortication was done fifteen months later, and this resulted in cure. The patient is now in good health.

CASE 20.—A white female, aged 9 years, was admitted in 1937. Empyema had occurred four years previously. The family physician had inserted a drain but had removed it in two weeks. A large cavity and draining sinus still persisted. After 3.5 months of preliminary drainage, an extensive one-stage rib resection and decortication were done. The patient went into severe shock and died within a few hours in spite of transfusion and other measures. It was felt that too much had been attempted at one time.

CASE 21.—A white female, aged 14 years, was admitted in 1938. Seven years prior to admission an acute illness resulted in empyema necessitans, and the child had been bedfast with draining sinuses since that time. The chief sinus had occurred anteriorly at the nipple. Chest deformity and finger clubbing were extreme. Posterior drainage was established in December. Rib resections were done in April and

in June. In October additional ribs were resected and a musculocutaneous flap thrown into the cavity. In March, 1939, she was discharged cured. It was noted that there was a definite recession of the clubbing of the fingers.

CASE 22.—A colored male, aged 49 years, was admitted in 1939. Empyema had been present for six months prior to entry. Establishment of adequate drainage led to cure although it was fifteen months until healing was complete. The patient has since died of carcinoma of the cecum.

CASE 23.—A white male, aged 13 years, was admitted in 1939. Empyema had occurred four years prior to admission. A physician kept a tube in the chest for ten days. A draining sinus had persisted, and the chest had become greatly deformed. After six months of preliminary drainage which included high-vacuum suction a two-stage rib resection was done with an eighteen-day interval intervening. This accomplished complete obliteration of a large cavity, and the patient was discharged cured after four months. He remains well.

CASE 24.—A white male, aged 15 years, was admitted in 1939. Three years prior to entry empyema had occurred. A physician inserted a tube drain which was removed after one month. The anterior, draining sinus had persisted. The chest had become badly deformed, and the fingers were clubbed. After five months of preliminary drainage a two-stage rib resection with a four-week interval resulted in cure. The boy was discharged two months later completely healed and remains well.

CASE 25.—A white male, aged 2 years, was admitted in 1939 with pneumonia. Closed drainage was followed by a bronchial fistula which necessitated keeping a drainage tube in place for twenty-three months when the fistula became obliterated and complete healing occurred. The child remains well.

CASE 26.—A white male, aged 71 years, was admitted in 1939 with pneumonia. An atypical acute interlobar empyema resulted. A drain was inserted, but a bronchial fistula has persisted since that time (two years). On one occasion two ribs were resected. It has been possible to keep the patient afebrile and in good health by seeing that a drainage tube remains in place. Because of the advanced age additional operative procedures are not contemplated. For a time malignancy was suspected, but as time goes on this seems less probable.

CASE 27.—A white male, aged 36 years, was admitted in 1940. Pneumonia six months previously had resulted in empyema which drained by way of the bronchial tree. There had been no surgical treatment. An immense cavity was present. Rib resection and open drainage resulted in complete cure in ten weeks, the patient gaining 58 pounds in weight during this time. He remains well.

CASE 28.—A white male, aged 26 years, was admitted in 1938. Chronic empyema, which had followed a stab wound of the chest, was cured only after several open thoracoplasties had been done and a musculocutaneous flap had been thrown into the cavity.

CASE 29.—A white female, aged 4 years, was admitted in 1940. This child had had three operations for empyema in six months prior to entry to this hospital. Under our care the draining sinus was dilated, and drainage then seemed adequate. However, a purulent pericarditis developed, and she died before other treatment could be instituted. There was no autopsy.

CASE 30.—A white female, aged 10 years, was admitted in 1940. Empyema had been present for one year, and on two occasions a rib had been resected to permit better drainage. A bronchial fistula led into a lower lobe which was the site of ex-

treme bronchiectasis. After a period of preliminary drainage lobectomy was done. It is thought that she is cured although not enough time has elapsed for us to be certain.

CASE 31.—A white male, aged 10 years, was admitted in 1940. Four years and nine months prior to entry empyema had occurred. A physician inserted a drain but removed it after two weeks. The sinus closed, but a second sinus appeared spontaneously and had been draining since that time. Chest deformity was extreme. A two-stage rib resection has apparently resulted in cure.

CASE 32.—A white male, aged 40 years, was admitted in 1940. Empyema was present for one year. The patient was cured by rib resection.

CASE 33.—A white male, aged 13 years, was admitted in 1940. Twelve years prior to admission empyema had followed pneumonia. A physician inserted a drain which was withdrawn after two weeks. During the intervening twelve years a sinus had persisted. On two occasions an operation had been performed. Deformity was slight and x-ray examination made on admission revealed a small empyema cavity in the chest. At operation, however, a cavity of fair size was exposed. A thorough decortication was done, and segments of four ribs were removed. This has apparently resulted in cure although the time interval is short.

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DISCUSSION

DR. FRASER B. GURD, Montreal, Quebec.—I am sure that many of you have had the experience that we have had with regard to empyema during the past three years; possibly some of you have not noted it.

It seems, however, that it is a matter in which this association might put itself upon record, namely, that whereas during the past three years since the sulfonamides have been applied in the treatment of pneumonia, of both lobar and lobular types,

the incidence of empyema has been much reduced, but, owing to the fact that patients with empyema who have been and who are being treated by means of sulfonamides are not sick, the physicians have seen little or no reason why they should be turned over to the surgeons until such time as the fibrinous exudate on the surface of the lung is beginning to be fibrous. We have had in consequence the experience; although we have not had but one chronic empyema produced as a result of this delay in drainage, of having more difficulty due to inadequate expansion of the lung during the past three years in Montreal General Hospital than we have ever had before.

DR. I. A. BIGGER, Richmond, Va.—I wish to defend decortication of the lung in the treatment of certain carefully selected cases of chronic empyema, for it preserves pulmonary function and avoids deformity. I realize that it is a shocking procedure, that there is apt to be a good deal of blood lost, and that, unless proper precautions are taken, the mortality rate will be relatively high. I think, however, that, if the patients for decortication are carefully selected, properly prepared for operation, and given adequate blood during and after the operation, the procedure can be done with only moderate risk.

Certain conditions must be met before decortication is recommended. Tuberculosis of the pleura must be ruled out. An attempt should be made to determine whether or not the lung will expand, and this is not always easy. If there are an obvious chronic fibrosis and atelectasis of the underlying lung, there is no object in removing the thickened pleura. Pleurobronchial fistula is probably a contraindication.

Although my experience has been limited to eight or nine cases, the results have been sufficiently good to make me feel that the procedure has a place in the treatment of chronic empyema. We did not have an operative death in this group, but one patient died several months later from tuberculosis which was probably activated by the operation. That is why I stress the necessity for ruling out a tuberculous infection of the pleura. We have done preliminary biopsies from the pleura in every instance, but the diagnosis of tuberculosis was not made from the biopsy specimen. Tuberculosis was discovered in the pleura removed at the time of decortication, and re-examination of the biopsy specimen revealed tuberculosis.

DR. CARL EGGERS, New York, N. Y.—When Dr. Singleton says the subject of chronic empyema is rather stale, we may agree with him. Nevertheless it is important to call attention to it from time to time because the condition is disabling and makes the patient a chronic invalid. In discussing the subject as much attention should be given to the underlying causes of chronicity as to the question of treatment because chronic empyema is most often due to the improper treatment of the acute condition and is therefore frequently avoidable.

The World War furnished an unusual opportunity to observe empyema in large series of cases. At that time I had occasion to study several groups in the acute as well as in the chronic stage. On the basis of this material it was found that the chief factors responsible for chronicity were imperfect drainage and persistent infection. By improving drainage and instituting Dakin Carrel treatment the great majority of chronic cases could be cured.

In the group resisting this type of treatment other causes of chronicity were looked for. They might be superficial, such as epithelialization of the drainage canal, osteomyelitis of a rib, or chondritis. Cure was obtained by removal of the offending focus. The causes held responsible for deep chronic empyema cavities were found to be contracted bottle-neck drainage openings; improperly placed drainage openings; pockets, recesses and separate cavities; infected lining membrane; rigid unyielding cavity; bronchial fistula; foreign bodies; tuberculosis; or general constitutional conditions.

In all such cases attempts were made to improve the general condition of the patient and at the same time keep the cavity clean with the aid of Dakin Carrel treatment. An operation was then done consisting of unroofing the cavity by resection of short pieces of ribs and removal of the parietal pleura. All recesses were opened or excised and the lung mobilized. This combination of mobilizing the chest wall as well as the lung makes deep breathing and free motion possible. One of the most important points in the after treatment is to get the patients out of bed early, even after the more extensive operations. They must be encouraged to carry on deep breathing exercises in front of a mirror, to keep their shoulders on the same level, and to do setting-up exercises. With such treatment bad deformities are avoided and the vital capacity of the lungs is increased over what it was prior to operation.

We operated upon 146 patients by this method and reported a mortality of 3.4 per cent.

Since that time I have performed a radical operation on twenty-six additional cases, with three deaths, a mortality of 12 per cent. The explanation for this increased mortality is probably to be found in the difference in cases; the group in civil life included neglected cases in older people whose resistance had been undermined by prolonged suppuration or who had other complications.

Many of the patients with chronic empyema are anemic and in poor general condition. For this reason it is important not to do too much at one time, but rather to divide the operation into several stages. With patience it is nearly always possible to bring about healing. Tuberculosis has to be considered in the very resistant cases.

I agree with Dr. Bigger.

DR. DUANE CARR, Memphis, Tenn.—Dr. Singleton is to be thanked for having brought before us a subject which is not so dramatic as others, but certainly affects more people.

Dr. Gurd has just mentioned some of the difficulties which are brought about by the indiscriminate use or the discriminate abuse of the sulfonamide drugs. One of those difficulties is that of obtaining a positive culture from the aspirated pus. All of us fear the bugbear of draining a pure tuberculous empyema with a tube, and we are frequently beset with the problem of deciding whether or not to drain a particular chronic empyema which has reached our hands.

The solution in our hands has recently been found—as no doubt some of the rest of you have found—in planting that pus in the peritoneal cavity of a mouse. Twenty-four to forty-eight hours later, in all but one of our cases, we found a virulent growing culture obtainable on sacrificing the mouse.

DR. RICHARD H. DIEFFENBACH, Newark, N. J.—I think it is very difficult to judge just when an empyema becomes chronic, and I want to thank Dr. Singleton for bringing up this subject, because I think it affects more people than most of the other things we have discussed.

Some years ago, I reviewed 114 cases of acute empyema which I saw personally. Most of them, I must say, were seen in consultation, so that for some reason or other they were not doing well or there would not have been a consultation.

The thing I want to bring out, and what impressed me, was that in those 114 cases of empyema, which we shall say were subacute at the time, we could demonstrate twenty-two cases of bronchial fistula. These were either demonstrated by injecting dye, or by making a bronchogram, or by the patient having expectorated the same type of pus as we obtained from the draining sinus.

When there is a bronchial fistula of this type, or any bronchial fistula, I think it is fair to assume there has been lung destruction, and, when there is lung destruction, you usually have an abscess underlying. If, of course, the empyema is originally putrid, I think you are safe to assume, as Dr. Neuhof pointed out, that you are undoubtedly dealing with an underlying putrid abscess.

However, there may be a nonputrid abscess underlying these cases, and I think it was shown in the twenty-two cases to which I have referred.

This leads me to suppose—and I may be wrong—that a chronic empyema is more a problem of treating the underlying lung lesion than it is a problem of treating the pleura. A discharging bronchus leading to an underlying suppuration will continually reinfect the pleura, and, of course, you cannot hope, so long as that persists, to bring about any cure so far as the empyema is concerned.

One other thing with which I was impressed was that in operating upon some of these chronic empyemas, one finds a perfectly smooth surface that looks like a clean, thickened pleura at the time of operation, whereas, say, in about a week, after the pack is removed, one will find numerous bronchial fistulas coming through. This, I think, is due to the fact that these bronchial fistulas are filled with granulation tissue, which at a later date frees itself.

In the treatment of chronic empyema, it is important to recognize early in the acute stage, if possible, the underlying lung lesion, and to control the latter by suitable means, thus preventing a chronic empyema.

In reply to Dr. Gurd's statement regarding the use of sulfonamides, I might state that one institution with which I am connected, in which they treat contagious diseases, we had a very severe measles epidemic about five years ago. At that time, during the winter, I had twenty-four acute empyemas. We had this past winter an epidemic of similar proportions, and I saw only one empyema.

DR. HOWARD LILIENTHAL, New York, N. Y.—There is something which has not been mentioned here which I think should be, and that is the matter of valve drainage. It does not signify how old the empyema is—it may have existed for years; if you will persist in treatment by true valve-drainage with a multifenestrated tube and finger-cot drain, there is a good chance of complete success without further operation. The drainage apparatus should be arranged so that, whenever the patient coughs, he blows air and fluid through the tube and, when he inhales, the valve will close and prevent air from entering the chest. The finger-cot valve should be arranged in a bottle and should not be immersed in any fluid, pus or other fluid. Under this treatment you will find that many of these chronic cases will be permanently cured. But you must not lose patience. It may take a few months but you may easily find out by x-ray while the patient is straining whether or not the visceral pleura is approaching the chest wall. Be sure, however, that you are not dealing with calcified pleura which is usually immobile; further surgical operation will then be required.

DR. FRASER B. GURD, Montreal, Quebec.—I wish to express my surprise that the largest collection of cases of chronic empyema ever treated, I am sure, by one person, has not been referred to. I refer to the cases and the method of treatment employed, treated in Walter Reed Hospital following the last war, or the first phase of the war, by Colonel Keller.

He used a method of decortication not with a scalpel but with a chemical. Those of you old enough to remember that period will remember that Colonel Keller treated the membrane over the lung by means of a saturated solution of gentian violet, which brought about necrosis. He was able to determine how many

hours' application was required to destroy 1 mm. thickness of the membrane. He then dissolved off the membrane after its necrosis had been brought about, by means of discontinuous irrigation with Dakin solution.

DR. ALBERT O. SINGLETON.—I am not familiar with the procedure of which Dr. Gurd spoke, but I think anything which would remove this membrane and not injure the lung, which is very difficult to do by dissection, would be very much welcomed.

Each case of chronic empyema is a separate problem. One gets cases which have lasted a short while or a very long time. Naturally, the treatment will be different in each one. Generally we have established a plan of beginning by trying the most conservative procedures, then doing the next most conservative or a little more radical, and so on, until finally the operations which have been spoken of by Dr. Bigger and Dr. Gurd, and others, of extensive removal of the outer wall as well as decortication, have been used.

But all in all, we feel that, when we have to go to the extent of a decortication, transplanting muscle, etc., it is a serious operation. We do not make any bones about getting donors and having blood ready to start transfusions on pneumonectomies before we start, but there is a tendency, I think, for us to keep working and digging in these empyema patients, disregarding the resistance and the amount of damage we are doing, until occasionally a fatality occurs, as has occurred with us. Thank you.

THE USE OF SULFANILAMIDE IN PARTIAL AND TOTAL RESECTION OF THE LUNG

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IN 1935, sulfamido-chrysoidine (red prontosil) was reported by Domagk to protect mice against the hemolytic streptococcus.[1] It was pointed out by him, however, that this chemical compound had no direct bactericidal effect. Later it was shown by Tréfouël and his associates that red prontosil became converted into p-aminobenzenesulfonamide (sulfanilamide) in the body.[2, 3] Sulfanilamide was equally as effective as red prontosil when given systemically and did have an in vitro effect upon hemolytic streptococci.[4-6]

The mechanism of action of sulfanilamide has not been determined. However, there is some evidence that sulfanilamide interferes with an essential metabolite of bacterial nutrition and prevents bacterial growth.[11] This action of sulfanilamide may be prevented by an "inhibiting substance," which is present in peptone, pus, and necrotic tissue.[12-14] A greater concentration of sulfanilamide is necessary for effective action in the presence of "inhibitor substances."[15] A sufficient concentration may not be obtained in the locale where it is desired with systemic use alone. If a high concentration could be obtained by local use at the site of bacterial growth, it should be of value in controlling the infection.

The local use of sulfanilamide, therefore, has a rational basis and has received considerable attention. It has been used with good results in the treatment of infected wounds[7] and as a prophylactic agent in clean and contaminated wounds.[8, 9] It is said that high concentrations of sulfanilamide are effective in the control of polymicrobic infections as well as infections with streptococci alone.[10]

One of the most common complications following complete or partial resection of the lung is empyema. This may result from soiling of the pleural cavity during operation or may occur later with the opening of a bronchus. The incidence of empyema following partial or complete resection of the lung has not been generally reported. O'Brien[16] reported fifteen one-stage lobectomies, all of which developed pleural in-

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fection. Blades and Kent[17] reported seven primary closures in eighteen partial resections of the lung, using individual ligation technique.

Prior to the use of sulfanilamide twenty lobectomies were performed by the authors from 1929 to 1938 on nineteen patients with suppurative disease of the lung. Postoperative empyema occurred eighteen times. One patient recovered without evidence of infection, and one died on the ninth postoperative day from uremia following a blood transfusion reaction. There was no evidence of empyema at necropsy. There were three additional deaths in the series. One patient died from hemorrhage, which was directly attributable to pleural infection. One death was due to cerebral abscess, and one, to mediastinal emphysema.

The use of sulfanilamide was begun in December, 1938. Since that time, fourteen partial resections of the lung for chronic pulmonary suppuration have been done on twelve patients. Postoperative empyema occurred eight times. Four patients recovered without clinical evidence of infection, and two died within twelve hours after removal of the second lobe in bilateral lower lobe lobectomies. In addition, five total resections of the lung have been performed in which sulfanilamide was used. Of these, one was done for chronic pulmonary abscess, and four, for neoplasm of the lung. Two of the latter had associated pulmonary suppuration. Empyema occurred postoperatively with one exception. This patient had a mixed tumor[18] of the lung without associated suppuration, and healing occurred without evident pleural infection. In none was there evidence of the bronchus having opened.

The operative methods varied in the two series of lobectomies. In the first series, without sulfanilamide, mass ligation of the hilar structures was done with the use of a tourniquet. In the second series, with sulfanilamide, six were done with individual ligation technique, and, of these, two healed without evident infection. Mass ligation of the hilar structures was done in the other six, and two of these healed without developing an empyema. In all the pneumonectomies the hilar structures were individually ligated. One of the five healed without evidence of pleural infection.

In the second series of seventeen patients, sulfanilamide generally was given the day preceding operation in dosage sufficient to produce a therapeutic blood concentration. Following operation systemic administration was continued in most cases until either the danger of infection had past, frank empyema had developed, or signs of toxicity had appeared. Seven patients were treated in this fashion, and three recovered without developing empyema. In the other ten patients, in addition to the systemic administration, sulfanilamide was used locally.* After removal of the diseased lobe or lung, 4 to 8 Gm. of sterile sulfanilamide crystals were spread over the hilar structures and dusted

*The operations for removal of the second lobe in Cases 1 and 8 are not considered here because of death within twelve hours.

TABLE I

PARTIAL RESECTION OF LUNG WITH MASS LIGATION AND TOURNIQUET TECHNIQUE

CASE	PATIENT	POSTOPERATIVE DIAGNOSIS	RESECTION AND DATE	SULFANILAMIDE (GM.)			CULTURE OF PLEURAL FLUID	OPEN DRAINAGE ESTABLISHED	RESULT
				PREOPERATIVE	LOCAL	POSTOPERATIVE			
1	L. S.	Bronchiectasis in left lower lobe	Left lower lobe, 2/1/39	1/31/39 to 2/13/39			Remained sterile	No	Wound healed. Improved
				4	0	36			
2	J. M.	Bronchiectasis in left lower lobe, and right middle and lower lobes	Left lower lobe, 6/5/39	6/ 4/39 to 6/18/39			*Alcaligenes faecalis*, 6/8/39	6/19/39	Wound healed
				5	0	41			
			Right lower and middle lobes, 10/23/40	10/22/40 to 10/23/40					Death 12 hours postoperatively. Anoxemia, pulmonary edema, metastatic encephalitis
				1	8	0			
3	E. W.	Bronchiectasis; right lower lobe, saccular; left lower lobe, cylindrical	Right lower lobe, 6/21/39	6/20/40 to 7/ 3/40			*B. mucosus-capsulatus, Alcaligenes faecalis*, 6/28/39	8/ 9/39	Wound healed. Improved
				5	0	41			
4	L. H.	Bronchiectasis in left lower lobe	Left lower lobe, 9/18/39	9/20/39 to 9/26/39			Sterile until 9/26/39 then *B. mucosus-capsulatus* was found	10/ 2/39	Bronchial fistula evident 12/16/39, but closed spontaneously; wound healed. Improved
				4	0	26			
5	J. P.	Bronchiectasis in right lower lobe	Right lower lobe, 1/31/40	1/30/40 to 2/17/40			*Hem. staphylococcus aureus* 2/6/40 Sterile, 2/8/40	No	Wound healed. Improved
				4	8	56			
6	C. B.	Teratoma of left anterior mediastinum	Part of left upper lobe, 2/26/40	2/27/40 to 3/ 2/40			Sterile until 3/4/40, when *Hem. staphylococcus albus* and *Hemophilus influenzae* were found	3/ 7/40	Bronchial fistula developed which was closed surgically. Wound healed. Improved
				0	8	11			

TABLE II

PARTIAL RESECTION OF LUNG WITH INDIVIDUAL LIGATION TECHNIQUE

CASE	PATIENT	POSTOPERATIVE DIAGNOSIS	RESECTION AND DATE	SULFANILAMIDE (GM.)			CULTURE OF PLEURAL FLUID	OPEN DRAINAGE ESTABLISHED	RESULT
				PREOPERATIVE	LOCAL	POSTOPERATIVE			
7	L. G.	Bronchiectasis in lower lobe of left lung and lower and middle lobes of right lung	Lower lobe of left lung, 9/27/39	9/26/39 to 10/ 4/39 5	7	13	Sterile until 10/4/39, then *B. coli* was found	10/ 8/39	Developed bronchial fistula which closed spontaneously. Wound healed.
			Lower and middle lobes of right lung, 10/25/40	10/24/40 to 10/25/40 3	4				Death 8 hours postoperative. Anoxemia, pulmonary edema, and metastatic encephalitis
8	E. K.	Bronchiectasis in left lower lobe (saccular type) and right lower lobe (cylindrical type)	Lower lobe of left lung, 9/29/39	9/29/39 to 10/ 4/39 5	0	13	Remained sterile	No	Wound healed. Improved
9	M. V.	Bronchiectasis in right upper lobe	Right upper lobe, 3/25/40	3/24/40 to 4/15/40 5	4	67	*Alcaligenes faecalis* was found, 3/27/40	4/ 3/40	Persistent bronchial fistula
10	A. M.	Chronic abscess in right upper lobe	Right upper lobe, 10/18/40	10/17/40 to 11/21/40 4	0	128	Sterile until 10/31/40; positive for diphtheroids; again sterile, 11/15/40	No	Wound healed. Improved
11	G. C.	Chronic abscess in right upper lobe	Right upper lobe, 10/30/40	10/30/40 to 11/13/40 5	8	63	Sterile; 11/1/40, bronchial fistula; 11/2/40, mixed infection	11/ 8/40	Bronchial fistula closed spontaneously. Wound healed. Improved
12	B. R.	Bronchiectasis in right lower lobe	Right lower lobe, 1/22/41	1/21/41 to 2/ 4/41 5	8	60	Sterile until 1/29/41; bronchial fistula, 1/29/41; mixed infection	2 /23/41	Bronchial fistula closed spontaneously. Small sinus still present

TABLE III

TOTAL RESECTION OF LUNG WITH INDIVIDUAL LIGATION TECHNIQUE

CASE	PATIENT	POSTOPERATIVE DIAGNOSIS	RESECTION AND DATE	SULFANILAMIDE (GM.)			CULTURE OF PLEURAL FLUID	OPEN DRAINAGE ESTABLISHED	RESULT
				PREOPERATIVE	LOCAL	POSTOPERATIVE			
13	F. B.	Bronchogenic carcinoma of left lung with gross suppuration	Left lung, 12/28/38	12/28/38 to 1/ 4/39			Sterile until 1/9/39, then *B. mucosus-capsulatus*	1/25/39	Partial thoracoplasty. Small sinus still present
				1	0	18			
14	E. B.	Mixed tumor of right lung; no gross suppuration	Right lung, 11/1/39	10/31/39 to 11/ 3/39			Remained sterile	No	Well; wound healed
				4	8	12			
15	H. R.	Chronic abscess of right lung	Right lung, 8/9/40	8/9/40			Positive 8/28/40. Nonhemolytic streptococcus	8/31/40	Thoracoplasty 10/16/40. Small sinus still present
				0	16	0			
16	W. S.	Bronchogenic carcinoma of right lung with gross suppuration	Right lung, 11/8/40	11/ 8/40 to 12/23/40			Sterile until 12/7/40, then pneumococcus Type XVII	12/24/41	Thoracoplasty 1/24/40. Small sinus still present
				0	8	152			
17	O. D.	Bronchogenic carcinoma of left lung; no gross suppuration	Left lung, 5/9/41	5/ 9/41 to 5/18/41			Sterile until 5/18/41, then *Staphylococcus aureus* was found	7/9/41	Thoracoplasty 8/13/41. Died 8/16/41 of hemolytic streptococcus wound infection and septicemia
				0	8	38			

into the pleural cavity. In one case 16 Gm. was used. Two of these patients recovered without infection of the pleural cavity.

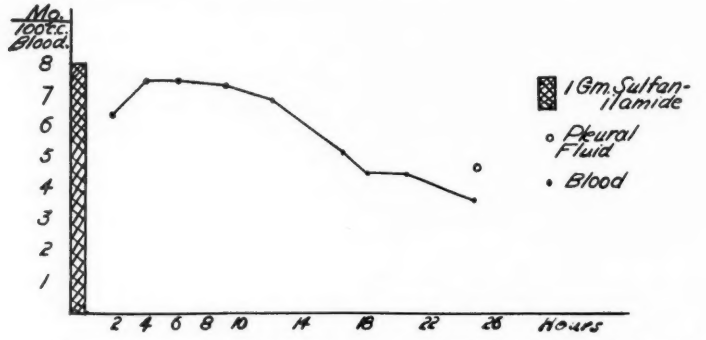

Fig. 1.—Blood and pleural fluid content after local implantation of sulfanilamide in the pleural cavity following pneumonectomy.

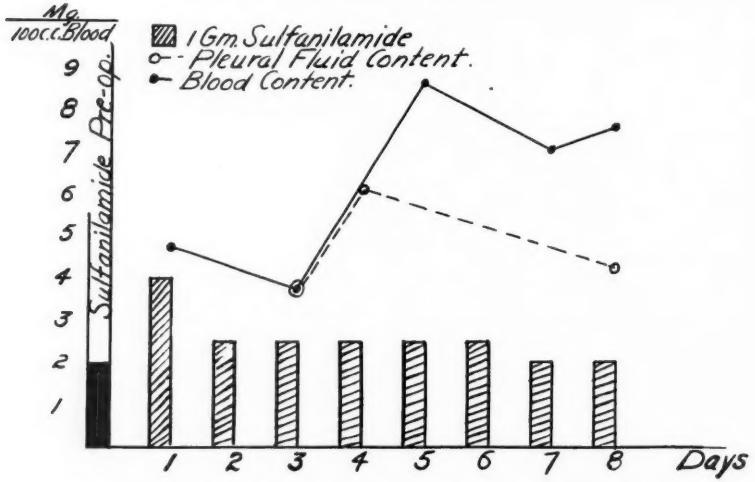

Fig. 2.—Blood and pleural fluid content after systemic administration of sulfanilamide.

Determinations of the sulfanilamide concentration of the blood or pleural fluid, or both, were made in all cases. A rapid absorption of sulfanilamide from the pleural cavity was noted in one case in which determinations were made every two hours after operation. A maximum concentration in the blood was reached in four to six hours (Fig. 1). This is in agreement with the findings of Marshall and his co-workers.[19] There was a definite tendency for blood and pleural fluid concentrations to vary in direct proportion to each other (Fig. 2, Fig. 3).

It is generally agreed that temporary closed drainage of the pleural cavity should be established following lobectomy for suppurative disease

of the lung. Where sulfanilamide was used locally such drainage rapidly lowered the concentration of sulfanilamide in the pleural fluid. Loss through drainage and rapid absorption of the drug from the pleural cavity brought the pleural fluid and blood concentration to the same level within twenty-four to forty-eight hours. However, the local use of sulfanilamide with the immediate high local concentration, even though temporary, should have a decided advantage over the systemic use of the drug alone. Because of its rapid absorption and the loss through drainage it is evident that the local use of sulfanilamide should be supplemented by systemic administration. The value of omitting drainage of the pleural cavity for the purpose of maintaining a high local concentration is yet to be determined.

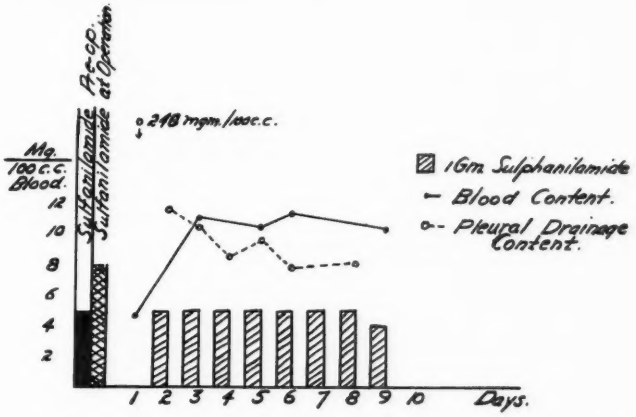

Fig. 3.—Blood and pleural fluid content after local and systemic use of sulfanilamide.

In the four patients who developed empyema following pneumonectomy, cultures of the pleural fluid became positive on the ninth, tenth, eighteenth, and thirtieth days. None of these patients developed bronchial fistulas. Eight patients developed empyema following lobectomy. Four of these had bronchial fistulas. In the other four, cultures of the pleural fluid, were positive on the third, seventh, seventh, and tenth days.

Cultures from the empyemas usually showed a mixed infection and a wide variety of organisms (Table IV). The fact that sulfanilamide did not prevent the growth of some of the organisms usually affected by the drug suggests that it was not present in sufficient concentration, that too great an amount of inhibiting substance was present, or that repeated gross contamination occurred from bronchial fistulas.

In the cases which did not develop bronchial fistulas, the infecting organisms were fewer in number and mostly of the varieties which do not respond to sulfanilamide (Table IV). An abundant growth of

B. coli was obtained in one case from pleural fluid that had previously been sterile. This patient was receiving adequate amounts of sulfanilamide and did not have a gross bronchial fistula when the empyema developed. A nonhemolytic streptococcus was isolated from an empyema following total resection of the lung for chronic abscess. In this case 16 Gm. of sulfanilamide were used locally at operation but none was given afterward. The infection became evident eighteen days postoperatively, obviously at a time when the effect of sulfanilamide had been lost. The other organisms listed in Table IV do not ordinarily respond to sulfanilamide treatment. It is possible that with some of the newer sulfonamide derivatives better results will be obtained.

TABLE IV

PRIMARY ORGANISMS CULTURED FROM INFECTED PLEURAL FLUID

ORGANISM	BRONCHIAL FISTULA (4 CASES)	NO BRONCHIAL FISTULA (10 CASES)	TOTAL
B. mucosus-capsulatus		3	3
Alcaligenes faecalis	1	2	3
Diphtheroids	2	1	3
Bacterium coli		1	1
Hemophilus influenzae	1		1
Staphylococcus albus	1		1
Pneumococcus Type XVII		1	1
Nonhemolytic streptococcus		1	1
Staphylococcus aureus		1	1

The use of sulfanilamide in thoracic surgery must be controlled as in other fields of surgery. Blood studies and urinalyses should be made frequently. While severe reactions may occur with the general or local use of the drug, there have been none in these seventeen patients.

CONCLUSIONS

It is rational to expect sulfanilamide to be of value in preventing pleural infection or in delaying its development following partial or total resection of the lung. With the use of sulfanilamide there has been a decrease in the incidence of pleural infection in this small group of cases. There is a free interchange of sulfanilamide between the pleural fluid and the blood stream. The nature of the pulmonary lesion and the operative technique play important parts in the development of pleural infection following partial or total resection of the lung. Bacteria encountered in pleural infections often are of those groups that do not respond to sulfanilamide, and other sulfonamides may be found to be more effective.

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DISCUSSION

DR. EVARTS A. GRAHAM, St. Louis, Mo.—I hope very much that these conclusions about the beneficial effect of sulfanilamide will prove to be correct.

Dr. Burford and I studied twenty-three cases of either partial or complete resection of the lung in which sulfanilamide was used locally, and, although there was no very striking difference between these cases and a similar number of controls, actually there were two or three more cases of empyema in those which had received the sulfanilamide, which indicated to us that probably it was not of great help, because the empyemas which occurred for the most part, in our opinion, occurred from two causes. One cause was the opening of the bronchus. If the bronchus stays closed, in our experience, one does not need to fear very much the development of a serious infection.

In the second place, the serious infections which occur in the pleural cavity after resection are due to organisms which so far there has been no evidence that the sulfonamide groups affect; at least, I am not acquainted with any such evidence. The organisms to which I refer are the necrotic, anaerobic, putrefactive organisms that cause the very severe damage.

In this series of twenty-three cases, seventeen were lobectomies for either uncomplicated bronchiectasis or chronic lung abscess, and one was a case of removal of a mediastinal dermoid and of the adherent upper lobe. These latter cases were drained by an intercostal catheter which, however, was kept clamped for twenty-

four hours. The other cases were not drained, four of which were total pneumonectomies. In some of the cases we got a reading of the pleural fluid concentration as high as 200 mg. per cent of sulfanilamide.

Within a few days in some of those cases, evidences of putrefactive infection occurred. These, however, were all accompanied by opening of the bronchus. We had hoped that perhaps the local use of sulfanilamide might prevent subsequent opening of the bronchus. Perhaps it does; perhaps a series of a couple of hundred cases in which it is used might show a considerable difference.

I hesitate to speak about this small series of ours of twenty-three cases, because it is not very conclusive, but I may say that six or eight months ago we abandoned the use of sulfanilamide locally because we felt that there just was not any particular benefit that we could see from it, regardless of whether the case was drained or was not drained.

We have not tried the local use of other sulfonamides. I do not want to be discouraging in the remarks I make, and I hope very much that these authors will go ahead and continue their work, because, of course, I think there is still a possibility that some of the other sulfonamides may be very helpful.

Certainly one would expect the intensive use of sulfonamides would perhaps tend to prevent some of the organisms which might cause infections, but to my mind those are not the organisms which cause the most serious damage.

DR. MAX PINNER, New York, N. Y.—There is just one point I should like to mention. We have used various sulfonamides in chronic tuberculous empyema, secondarily affected with streptococci or staphylococci, with good results as far as the secondary infection is concerned.

In these empyemas, however, it is very striking that there is no free interchange between pleural fluid and blood. When these patients received large doses of sulfonamide drugs by mouth, we never could find any measurable amount of sulfanilamide in the pleural fluid. And when they were given large doses of sulfonamides intrapleurally, the blood level never was more than just above the determinable traces, so that one may not simply go on the assumption that this free interchange always exists.

If the pleura is thickened by chronic processes, there is no interchange between pleural fluid and blood.

DR. RICHARD H. MEADE, JR., Philadelphia, Pa.—I have been interested in the discussion of the local use of sulfanilamide in lobectomy cases. I am sorry Dr. Bigger has left, because in April, when I visited him in Richmond, he reported to me, as did Dr. Vinson, that during bronchoscopies they were using sulfanilamide powder for insufflation of the bronchi, not only in the treatment of inoperable bronchiectasis, but also in preparation for lobectomy in bronchiectasis.

Having heard the report of this work, and through the collaboration of Dr. William Lell, a bronchoscopist, in Philadelphia, we have carried out some experiments to determine the absorption of sulfathiazole from the bronchial mucosa and the excretion of the drug into the bronchi when given by mouth.

The work is not far enough advanced to have any actual value. In two cases, however, sulfathiazole was given by mouth. In each case 7 Gm. were given during the course of twenty-four hours. In one the blood level reached 7.8 mg., and the level in the bronchial secretion removed by bronchoscopy was 1.8. In the other patient, the blood level reached after giving the same amount of drug by mouth was 2.4, and the level reached in the bronchial secretion was 1.2.

It was thought there might be some error in the examination of the sulfathiazole content in the bronchial material, so that a control was run on a known amount of

sulfathiazole placed in the secretion removed from a patient who had not been receiving the drug.

I know that Dr. Tucker and Dr. Atkins at the University of Pennsylvania have been doing similar work, using sulfadiazine, insufflating that into the bronchi. So far as I know, there has been no report of the excretion into the bronchus of a patient when the drug was given by mouth.

It seems to me that, if a high enough level can be reached so that the bronchial stump would be more or less sterilized, the risk of empyema following lobectomy would be considerably lessened.

A short time after this discussion the passage of sulfadiazine into the bronchial secretions of a patient with bronchiectasis was done with the help of Dr. Lell. Ten grams of the drug were given by mouth during a period of twenty-four hours. The blood level was found to be 14 mg. per cent, and two hours later material aspirated from the right lower lobe bronchus showed a sulfadiazine content of 13.3 mg. per cent. The determination of the sulfadiazine content of the bronchial material was checked against a sample of similar material from another patient containing a a measured amount of sulfadiazine.

EXPERIMENTAL OBSERVATIONS ON THE USE OF DRUGS OF THE SULFONAMIDE GROUP IN THE PLEURAL SPACE

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LOCAL application of one or another of the members of the sulfonamide group of drugs has received widespread trial and the results, while not yet completely evaluated, have been sufficiently encouraging to justify some measure of clinical application. Since pleural infection remains as the final great obstacle to be overcome in the surgery of the interior of the thorax, it is logical that the local use of these drugs at operation would be investigated to the limit. Simultaneously with the adoption of clinical investigations of this problem, experiments were undertaken upon laboratory animals in order that controlled results might be achieved.

The infection which follows pulmonary resection for suppurative disease constitutes a major clinical problem to be met by the thoracic surgeon. Infections of this sort are characterized by a multiplicity of microorganisms, the usual flora including both aerobic and anaerobic bacteria. Members of the spirochetal and the fusiform groups of organisms are extremely common under such conditions, and additional frequent invaders include the *B. melaninogenicum*, aerobic and anaerobic streptococci, staphylococci, diphtheroid bacilli, and a host of other microorganisms which defy identification.

Since the clinical problem presents a complex bacteriologic picture, it seemed wise to study the relative effectiveness of several of the members of the sulfonamide group of drugs and, again because of the mixed infection, to observe the results of mixed or combined chemotherapy. The drugs selected for trial included sulfanilamide, sulfapyridine, sulfathiazole, and sulfanilylguanidine. The methods of the investigation were as follows.

Normal dogs weighing from 7 to 9 kilograms were employed throughout. Arbitrary amounts of 4.0 Gm. of either drug and 1 Gm. of each drug were decided upon, and these amounts were employed in all experiments. Five dogs were subjected to a study of the results of the implantation of 4 Gm. of each drug and 1 Gm. each of all four drugs respectively, into the uncontaminated, virgin pleural cavity. Aseptic

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TABLE I

TABULATION OF RESULTS OF THE INVESTIGATION OF THE RELATIVE EFFECTIVENESS OF FOUR MEMBERS OF THE SULFONAMIDE GROUP OF DRUGS IN PREVENTING DELIBERATELY PROVOKED EMPYEMA THORACIS IN DOGS

(The mixed flora of the infected material is shown.)

GROUP	BACTERIOLOGIC FLORA	DOG					
		1	2	3	4	5	6
A	(Aerobes) Diphtheroid bacilli, *Staphylococcus albus*, streptococci	Control Dog, 2 c.c. pus	2 c.c. pus, 4 Gm. sulfanilamide	2 c.c. pus; 4 Gm. sulfapyridine	2 c.c. pus; 4 Gm. sulfathiazole	2 c.c. pus, 4 Gm. sulfanilylguanidine	2 c.c. pus, 1 Gm. of each of 4 drugs
	(Anaerobes) *B. fusiformis*, spirochetes, staphylococci, streptococci, *B. melaninogenicum*	Empyema thoracis fatal on 9th day	Autopsy 24th day, no empyema	Distemper fatal 9th day, no empyema	Autopsy 24th day, no empyema	Autopsy 24th day, no empyema	Autopsy 24th day, no empyema
B	(Aerobes) Diphtheroid bacilli, *Staphylococcus albus*, streptococcus, Gram-negative rods	Control Dog 2 c.c. pus	2 c.c. pus, 4 Gm. sulfanilamide	2 c.c. pus, 4 Gm. sulfapyridine	2 c.c. pus; 4 Gm. sulfathiazole	2 c.c. pus, 4 Gm. sulfanilylguanidine	2 c.c. pus, 1 Gm. of each of 4 drugs
	(Anaerobes(Gram-positive rods, staphylococci, *B. fusiformis*, spirochetes	Empyema fatal on eighth day	Autopsy 21st day, no empyema	Autopsy 21st day, no empyema	Autopsy 21st day, no empyema	Autopsy 21st day, no empyema	Autopsy 21st day, no empyema
C	(Aerobes) Diphtheroid bacilli, *Staphylococcus albus*, Gram-positive rods	Control Dog 2 c.c. pus	2 c.c. pus, 4 Gm. sulfanilmide	2 c.c. pus, 4 Gm. sulfapyridine	2 c.c. pus, 4 Gm. sulfathiazole	2 c.c. pus, 4 Gm. sulfanilylguanidine	2 c.c. pus, 1 Gm. of each of 4 drugs
	(Anaerobes) Staphylococcus, spirochetes, *B. fusiformis*, *B. melaninogenicum*	Empyema fatal on 11th day	Autopsy 28th day, no empyema	Autopsy 28th day, no empyema	Autopsy 28th day, no empyema	Autopsy 28th day, no empyema	Autopsy 28th day, no empyema
D	(Aerobes) *Staphylococcus albus*, streptococcus, *Staphylococcus aureus*, Gram-negative rods	Control Dog 2 c.c. pus	2 c.c. pus, 4 Gm. sulfanilamide	2 c.c. pus, 4 Gm. sulfapyridine	2 c.c. pus, 4 Gm. sulfathiazole	2 c.c. pus, 4 Gm. sulfanilylguanidine	2 c.c. pus, 1 Gm. of each of 4 drugs
	(Anaerobes) Spirochetes, *B. fusiformis*, streptococcus, Gram-positive rods, Gram-negative rods	Empyema fatal on tenth day	Autopsy 26th day, no empyema	Autopsy 26th day, no empyema	Autopsy 26th day, no empyema	Autopsy 26th no empyema	Autopsy 26th day, no empyema

technique was observed at all times, and a small intercostal incision was made under positive pressure intratracheal respiration with intravenous nembutal anesthesia. The drug was deposited within the pleural cavity; the lungs were re-expanded; and the wound was closed tightly in anatomical layers. No special further precautions were observed.

In the study of the effectiveness of the drugs in the prevention of infection, similar normal dogs were employed. There were four groups of these dogs, each comprised of six animals. The above technique was used. The pleural cavities were deliberately contaminated, and, at the same time, local application of chemotherapy was effected.

The infected material employed to produce contamination of the pleura consisted of pus obtained from clinical cases of putrid empyema following pulmonary resection for suppurative disease. The purulent material was kept warm after collection, submitted to careful bacteriologic study, and employed for experimental purposes without delay.

The procedure was identical in each group of experimental animals, namely, 2 c.c. of pus were placed within the pleural cavities of every dog; one dog was used as a control while the remaining five dogs were subjected to direct, simultaneous intrapleural application of 4.0 Gm. of sulfanilamide, 4.0 Gm. of sulfapyridine, 4.0 Gm. of sulfathiazole, 4.0 Gm. of sulfanilylguanidine, and a combination of 1 Gm. of each drug respectively.

The bacteriologic flora of each specimen of pus was studied under aerobic and anaerobic conditions, and the results are shown in Table I. This table also reveals the outcome of the experimental studies which were described above. The cultures and bacteriologic examinations were all made by Harold H. Mitchell, a graduate student in the Department of Bacteriology, who has had an extensive experience with the organisms found in pulmonary infections.

RESULTS

The first group of dogs received local application in the pleural cavity of 4 Gm. of each of four sulfonamide drugs and a combination of 1 Gm. of each drug respectively. None of this group manifested any untoward reaction as a result of the procedure. All were autopsied three weeks later, and the sole observation made was the presence of extensive adhesions between the parietal and visceral pleural surfaces.

The remaining four groups of dogs were submitted to deliberate contamination of the pleural cavity, and, of each group, one animal was employed as a control while the remaining five were given simultaneous implantations of 4 Gm. of one of the four drugs and of a combination of 1 Gm. of each drug, respectively. In every instance the control dog

died of an empyema thoracis within eleven days. No bacteriologic studies were made on the pus found within the thorax because every dog died at some time during the night and autopsy was therefore delayed for an unknown period of time.

The most significant finding was that not one dog which received intrapleural sulfonamide therapy died of empyema. True, one dog which had received pus and 4 Gm. of sulfapyridine died on the ninth day of a pneumonic form of distemper, but the autopsy revealed no empyema whatever. The remaining dogs were autopsied at intervals of from three to four weeks after the experiment had been performed, and none revealed the presence of intrapleural infection. In each instance extensive pleural adhesions were present which were comparable to those seen in the uninfected group of animals. While the control dogs were desperately ill before death, not one of the other animals gave any evidence of sickness following the experiment.

COMMENT

Deliberate contamination of the pleural cavities of dogs with pus of a mixed flora resulted in a fatal empyema in every instance. On the other hand, identical contamination of the pleural cavities in other dogs failed to result in an empyema when simultaneous local application of various members of the sulfonamide group of drugs was employed. There was no apparent superiority of any one drug over the other, and the use of any single member of the group appeared to be as effective as a combination of all four drugs. The dosages of the drugs were admittedly relatively great, and it might be profitable to pursue similar studies with gradually decreasing amounts of these chemicals.

Such satisfactory results have not attended the clinical use of similar procedures and the explanation seems to be that these experiments are not comparable with the conditions present after pulmonary resection for suppurative disease. There certainly exists a different problem when a continued source of infection is present, such as from a leaking bronchial stump or from a mass of devitalized, infected tissue.

These results may not be interpreted to indicate that local sulfonamide therapy will be efficacious in combating an established empyema thoracis. They do indicate, however, that such measures should be effective in the control of infection after intrathoracic procedures which do not provide a continued source of contamination following the operation.

It may be of interest to add that the wounds of each experimental animal healed per primam. Small amounts of the drugs were sprinkled on the wound surfaces when the experiments were made, and it seems reasonable to attribute, in part at least, the absence of wound infection to these chemicals.

Finally, it seems worth while to call attention to the adhesion-forming potentialities of drugs in this group. It may be that this characteristic will make indiscriminate use of these chemicals in the abdomen undesirable. It also may be that these materials will prove efficacious in the deliberate production of pleural adhesions, such as for the purpose of poudrage through the thoracoscope preliminary to lobectomy, or to bring about fusion of pleural surfaces in certain of those patients subject to recurring spontaneous pneumothorax.

THE LOCAL USE OF SULFANILAMIDE IN THE PLEURAL CAVITY

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VERY soon after its meteoric rise to therapeutic prominence, sulfanilamide began to intrigue surgeons with its possible efficacy as a bactericidal agent when applied locally. Early studies in this regard were deferred largely because the first concepts of the mode of action of the drug held that its therapeutic properties were the result of a rather intricate set of reactions between the drug and the host with a resultant altered immunal capacity. Although in the main theoretical, this reasoning led for a time to the uncontested assumption that the drug was without significant effect when applied locally. While the exact mode of action of the entire sulfonamide group is still obscure, in vitro experiments have shown that sulfanilamide, when applied to an inoculum, may be highly bactericidal if the concentration is sufficient. Further it has been shown that the drug varies in effectiveness in different media.

Early in 1939 Jensen, Johnsrud, and Nelson[1] published a very striking series of compound fractures in which sulfanilamide had been implanted in the wounds at the time of operation. In a large, well-controlled series these workers were able to report the very significant reduction of wound infections from 27 per cent to 5 per cent. Experimental and clinical evidence that the drug was without deleterious effect on the healing of tissue when applied locally was soon forthcoming. Key and his co-workers[2, 3] have studied the healing processes and tissue responses when sulfanilamide crystals are implanted and have shown that no damage results from its use in bone, synovial membrane, muscle, or tendon. Thompson, Brabson, and Walker[4] have recently published their experience with sulfanilamide implanted in the peritoneal cavity in cases of acute appendicitis with peritoneal involvement. They have observed beneficial effects on the disease and were able to find no deleterious effects on the tissues.

The incontestable establishment of the drug as a valuable adjunct in the prophylaxis of infection in clean or potentially infected wounds is

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a problem that does not permit of adequate experimental approach and must of necessity await carefully evaluated statistical studies of large groups of cases.

In view of the high concentrations of the drug which develop in the tissues when the crystals are implanted locally (Jensen, Johnsrud, and Nelson[1] report concentrations above 200 mg. per cent lasting for thirty hours or more when 5 to 10 Gm. were used), and because the crystals are without apparent damage to serous membrane,[3, 4] we have been led to study the effect of the drug when introduced into the pleural cavity after intrathoracic operations. The value of any agent which would decrease the incidence of, or favorably influence the course of, postoperative empyemas is too apparent to those engaged in thoracic surgery to need further comment. Likewise, the difficulties in evaluating a study of this sort will be readily apparent to those familiar with the vagaries of pleural infections and the problems of the "open bronchus."

Thus far we have had an opportunity to use the drug locally in twenty-three cases. Of these, sixteen were lobectomies for lobar suppuration, four were total pneumonectomies, one was an excision of a mediastinal dermoid, one was an excision of a dermoid with amputation of the upper lobe, and one was a lingulectomy for bronchiectasis confined to the lingula of the left upper lobe. Of the four total pneumonectomies, one was for universal bronchiectasis, two were for bronchiogenic carcinoma without appreciable pulmonary suppuration, and the fourth was done for a bronchiogenic tumor with extensive pulmonary suppuration. The lobectomies were, with one exception, done for bronchiectasis or chronic lung abscess with associated bronchiectasis. Five of the patients were children.

We used the commercial crystals which were autoclaved for twenty minutes in our own operating room. Concentration studies on standardized solutions of the autoclaved drug show it to be virtually unaltered by this method of sterilizing. The operative technique has varied of necessity. Whenever possible the technique of individual ligation has been employed in the lobectomies. This procedure has been well described in a recent paper by Blades and Kent.[5] Similarly in the total pneumonectomies the hilum structures have been dealt with individually whenever possible. When the case did not lend itself to such treatment, then mass ligation of the hilum was done. At the completion of the operation and after the toilet of the cavity had been completed, the crystals were dusted into the pleural cavity, care being taken to cover the bronchial stump well and to cover the dependent posterior gutter where soiling was usually maximal. It was our routine to institute intercostal drainage at the time of operation in all cases of lobectomy; consequently, all the lobectomy cases received primary intercostal drainage regardless of the technique employed on the hilum. Likewise it was our practice never to employ primary drainage in total pneumonec-

tomies, and thoracotomies for mediastinal tumors, unless it appeared that an empyema was unavoidable. In order to assure a satisfactorily high concentration of the drug locally in cases which were drained, the tubes were kept clamped for periods of six to twenty-four hours postoperatively. Early in the study concentrations were not taken routinely, but in the later cases it has been our practice to obtain blood sulfanilamide concentrations at twenty-four-hour intervals until the drug disappeared from the blood. We obtained, when possible, cultures of the predominating organisms present in the suppurative pulmonary process preoperatively and also the organisms predominant in the postoperative suppurative complications for correlative purposes.

The amount of the drug introduced has varied from 2 to 15 Gm., the amount depending on the size of the patient, the degree of suppuration present, and the extent of the contamination. The data on these twenty-three cases are summarized in Table I. Eight patients did not develop empyema, and, of these, none had an open bronchus at any time. Fifteen developed putrid pleural infections, all associated with open bronchi, either transient or persistent. An examination of Table I will reveal that in no instance did a putrid empyema develop in a case in which the bronchus remained completely and permanently closed. Conversely, all cases in which bronchial openings occurred did develop putrid pleural infections. In no instance did the previous implantation of the drug prevent the development of empyema once an open bronchus had supervened. In several instances we have seen the streptococcus component of the empyema flora absent after the previous implantation of the drug had been carried out, but in no way could it be felt that the empyema was any less severe or chronic.

This series closely parallels any previous group of cases that we can pick from our series in that patients with an open bronchus invariably develop putrid infections of the pleura. Whenever the bronchus can be secured individually and closed by interrupted silk sutures, the bronchus will usually stay closed permanently and empyema will not develop, regardless of whether or not sulfanilamide is implanted locally, unless contamination of the pleura has been gross at the time of operation.

We do feel that the local use of the drug is indicated where contamination of the pleura has been rather extensive, but where the bronchus has been secured in such a fashion that a reasonable chance exists of its staying closed. In these cases we feel that the local implantation of the drug provides at the *locus minoris resistentiae* a bacteriostatic medium which will hold the infective contaminants in check until the normal defense processes can recuperate. The fact that in this series of cases the technique of individual ligation was applicable in such a small percentage is evidence of the type of case with which we most frequently deal; many of the cases have been classed as inoperable by others, and

TABLE I

CASE	AGE (YR.)	DIAGNOSIS	OPERATION TECHNIQUE	AMOUNT OF DRUG (GM.)	POST-OPERATIVE PERIOD (HOURS)	BLOOD CONCENTRATIONS (MG. %)	EMPYEMA
J. R. P2321	11	Bronchiectasis	Lobectomy; individual ligation	6	24 48	5 Trace	None
D. M. G1443	3	Foreign body	Lobectomy; individual ligation	5	No determination		None
J. L. H1962	14	Bronchiectasis	Lobectomy; individual ligation	5	24 96	1.3 0.8	None
W. T. 84106	39	Bronchiectasis	Lobectomy; mass ligation	15	24	9.1	Putrid
A. M. 83694	30	Bronchiogenic carcinoma	Total pneumonectomy; individual ligation	2	24 48	2.6 Trace	None
L. C. 51465	20	Bronchiectasis	Lobectomy; individual ligation	10	24 48 72	8.3 2.8 Trace	None
I. H. 81992	24	Mixed tumor of lung with marked pulmonary suppuration	Total pneumonectomy (2-stage); mass ligation	10	No determination		Putrid
K. R. 83238	41	Bronchiectasis; chronic lung abscess	Lobectomy; mass ligation	10	No determination		Putrid
J. T. 83779	35	Bilateral bronchiectasis	Total pneumonectomy (2-stage); mass ligation	15	24 48 72	10.0 4.7 3.2	Putrid
M. C. A8189	33	Bronchiectasis	Lobectomy; individual ligation	10	24	14	None
M. S. A8387	21	Chronic lung abscess	Lobectomy; mass ligation	12	24 48 72 96	14.5 4.5 1.0 None	Putrid
A. M. A8325	56	Bronchiectasis bilateral	Lobectomy; mass ligation	12	24 48 72 96 120	16.6 7.6 4.1 1.9 0.3	Putrid
DeJ. A9363	24	Mediastinal dermoid with pulmonary fistula	Excision of tumor; upper lobe lobectomy; mass ligation	12	24 48 72 96	15.4 3.9 0.9 0.3	Putrid
P. S.	9	Bronchiectasis	Lobectomy; mass ligation	5	24 48 72	2.9 0.4 None	Putrid
E. H. 84986	21	Mediastinal tumor	Excision of tumor	5	No determination		None
I. C. 87358	40	Chronic lung abscess	Lobectomy; mass ligation	15	24 48	5.8 Trace	Putrid

TABLE I—CONT'D

CASE	AGE (YR.)	DIAGNOSIS	OPERATION TECHNIQUE	AMOUNT OF DRUG (GM.)	POST-OPERATIVE PERIOD (HOURS)	BLOOD CONCENTRATIONS (MG. %)	EMPYEMA
B. C. 82272	24	Lung abscess	Lobectomy; mass ligation	15	24 48 72	14.2 4.1 0.3	Putrid
J. S. 87324	36	Bronchiectasis	Lobectomy; mass ligation	15	24 48 72	5.0 1.8 1.3	Putrid
J. M. 87396	25	Bronchiectasis left lingula	Lingulectomy; mass ligation	10	24	6.1	Putrid
A. B.	60	Carcinoma of lung	Total pneumonectomy; individual ligation	5	24	3	None
S. W.	7	Bronchiectasis bilateral	Lobectomy; mass ligation	6	24 48 72	3.2 Trace None	Putrid
D. W. B1443	26	Bronchiectasis	Lobectomy; mass ligation	15	24 48 72	8.1 4.0 None	Putrid
W. F. R211	11	Bronchiectasis	Lobectomy; individual ligation	5	24 48 72	4.1 2.4 Trace	None

their cure is often pure salvage. Naturally a series of this type will run high in the number which have to be treated by the mass ligation technique.

These two points, (1) the inevitable occurrence of putrid infection in the presence of an open bronchus and (2) the probable beneficial influence of the drug when contamination of the pleura is gross, are well illustrated by the case of J. T. 83779, on whom a total pneumonectomy was done for universal bronchiectasis. It was necessary to do the procedure in two stages because of a very adherent pleura, and at the second stage the patient's poor condition necessitated quick completion of the operation with a mass ligation of the hilum structures. Contamination was of necessity considerable. The patient's immediate postoperative course was uneventful, the rectal temperature never exceeding 37.8 for the first ten days. At this time he developed a small bronchial opening and proceeded to get a putrid empyema, which was tolerated without incident.

In all instances where sulfanilamide concentration determinations were made on the pleural fluid itself, values above 200 mg. per cent were found during the first twenty-four hours.

The figures in Table I showing the blood concentrations are striking and demonstrate the marked efficiency of the pleura as an absorbing mechanism. The drug is absorbed rapidly, a peak being reached during the first twenty-four hours. After this the curve drops rapidly until,

at the end of seventy-two to ninety-six hours, there is no drug left in the blood stream. Concentrations above 10 mg. per cent are commonly achieved during the first twenty-four hours. The highest value we have yet obtained was 16.6 mg. per cent. In this connection it is interesting to note the figures of blood concentrations in peritoneal cases as given by Thompson and his associates.[4] The concentrations in our pleural cases are consistently higher than those obtained when the drug was placed in the peritoneal cavity. However, the factors, such as drainage, are too variable to permit of any conclusive comparisons. Such concentrations are well above the therapeutic levels striven for when the drug is given orally and indicate that we have by the local implantation method a two-edged therapeutic sword for the prophylaxis of infections; viz., a local concentration at levels bacteriostatic even for organisms resistant to sulfanilamide in ordinary concentrations, and a reservoir from which the drug is rapidly absorbed, giving therapeutically high hemic concentrations. Of course, this relation is short lived, the local concentration being rapidly depleted by the efficient absorptive mechanism of the pleura.

Because of the very high blood concentrations we have consistently obtained, and because of the serious results that may occur when sulfanilamide is given to a patient hypersensitive to it, we have felt obliged to test each preoperative candidate by giving a trial dose of the drug before operation. Thus far we have seen no ill effects from the local implantation of the crystals into the pleural cavity.

So firmly have we become convinced of the inefficacy of sulfanilamide when implanted into the pleural cavity when there is a probability of an open bronchus supervening that recently we have been omitting its use with the exception of a few cases. These have been cases in which contamination was gross at the time of operation, but in which a good bronchial closure was obtained. Thus far we have had no postoperative empyemas develop in cases in which the drug was not used and in which the bronchus remained closed.

SUMMARY

1. Sulfanilamide crystals have been placed locally in twenty-three major thoracic cases, including four total pneumonectomies, sixteen lobectomies, two mediastinal cases, and one lingulectomy.

2. Blood concentrations reveal the striking efficiency of the pleura as an absorptive mechanism. Levels as high as 16.6 mg. per cent are obtained, the peak being reached during the first twenty-four hours. After this the level falls off rapidly. The concentrations found in the pleural fluid are all above 200 mg. per cent during the first twenty-four hours.

3. We believe that the implantation of sulfanilamide crystals into the pleura after intrathoracic operations will not prevent or even minimize

a putrid empyema if the bronchus opens. Where contamination at the time of operation is rather gross, but where the bronchus may be reasonably expected to remain closed, the drug very likely has value in preventing an empyema.

4. Thus far we have had no ill effects from the administration of the drug, which has been implanted in amounts as high as 15 Gm.

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GIANT CELL TUMOR OF THE TRACHEA

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CASE HISTORY

On March 22, 1940, we were consulted by an unmarried Argentinian, 25 years of age. His illness had commenced six months previously with a severe cold, which was followed by a persisting catarrh, with occasional sense of a whistling sound in the chest particularly audible during periods of catarrhal exacerbation. On one occasion, in November, 1939, he suffered an attack of fever and dyspnea, lasting about ten days, which was diagnosed as of pleural origin. After this attack symptoms continued and the patient was treated as an asthmatic in spite of negative response to the skin tests applied. A week before our examination, he began to suffer from cough, generally dry, and likely to occur at any hour. One of these attacks, occurring while the patient was in our consultation rooms, terminated in hemoptysis, with the expulsion of pure blood.

Physical examination disclosed in the right hemithorax a general increase in percussion note with diminution of vocal fremitus and breath sounds, these three signs being manifest chiefly in the posterior and inferior part. There were no râles.

The patient brought several chest x-ray films with him, one of which was taken at the time of the diagnosis of pleural involvement (Fig. 1). A dense shadow was apparent at the right base, and a small pneumothorax extended from apex to base; there was a small but unmistakable fluid level in the pneumothorax space. In later roentgenograms a gradual decrease of these abnormalities was evident, with their final disappearance at the end of a month. In the x-ray film made on the day of our first examination, four months after the first film was taken, a fact of great interest was learned. Not only had the dense basal shadow disappeared, but the zone where the shadow had previously been evident, and, in fact, the entire lower lobe, were more clear than the opposite lung, so that the bronchovascular markings could hardly be seen (Fig. 2).

Symptoms, clinical signs, and the roentgenological appearance combined to suggest the existence of an intrabronchial tumor. In addition to the cough with little or no expectoration and hemoptysis, there was the whistling sound "heard at the open mouth, not at the chest wall," which, as Chevalier Jackson[1] has noted, "is usually the earliest symptom and is almost always present later."

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Significant among the clinical indications were the absence of bronchial secretion and spasm, justifying the diagnosis of asthma, and the finding of the syndrome of localized emphysema, attributable to an in-

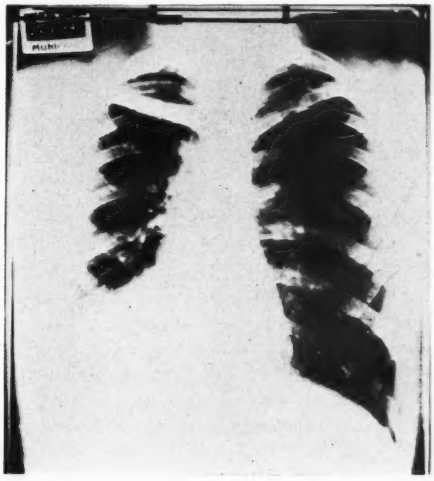

Fig. 1.—Roentgenogram of Nov. 16, 1939, showing atelectasis of the middle and lower lobe of the right lung and deviation of the trachea to the right. The pneumothorax and fluid level are not visible in the reproduction.

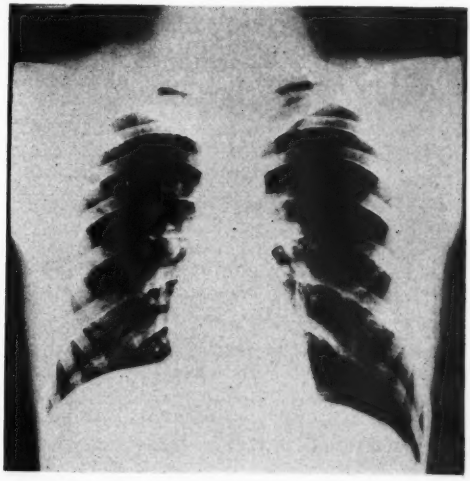

Fig. 2.—Roentgenogram of March 22, 1940. The atelectasis has disappeared, and the trachea is in normal position. The bronchovascular markings are less prominent in the right than in the left lung.

trabronchial mass obstructing the respiration. The roentgenograms were unquestionably of great importance (Figs. 1 and 2). They really showed phases of atelectasis and emphysema, in order inverse to that

commonly occurring in the evolution of intrabronchial tumors, but in a manner perfectly possible since the phases are reversible. When the tumor is not of sufficient size to obstruct a bronchus completely, the accumulation of a certain amount of bronchial secretion is necessary to effect closure. Once this is overcome, the exchange of air is partially re-established, atelectasis disappears, and emphysema follows. On the other hand, the latter should have been present in our case before the occurrence of atelectasis of the middle and inferior lobes, since in the first roentgenogram a pneumothorax was visible, resulting without doubt from the rupture of a vesicle in the emphysematous lung, as made clear by Westermark.[2] Actually the succession of atelectasis and emphysema, as noted in the x-ray films, is a sign of primary importance in the diagnosis of intrabronchial tumor; attention has been called to its manner of development and the importance of the alternating signs (Westermark,[2] Chevalier Jackson[3] and Overholt and Rumel[4]).

Bronchoscopic Examination.—The existence of an intrabronchial tumor being suspected, bronchoscopic examination was ordered and carried out on March 24. At the level of the right inferior main bronchus the bronchoscopist encountered a tumor mass, from which he removed a small piece for biopsy. Immediately, on this manipulation, a violent hemoptysis followed, which lasted several minutes. This was easily explained, as was seen later, by the nature of the tumor. From then on the patient was very dyspneic; during the afternoon of the same day he developed massive collapse of the right lung. On the following morning signs of mediastinal emphysema were apparent, and in spite of all medical and surgical recourse, he died on the next day.

The facts disclosed by necropsy follow:

Macroscopic Description.—When the trachea was opened longitudinally along its posterior surface, a piriform tumor was found at the level of the bifurcation, measuring 2 by 5 by 4 cm. It was seated on the tracheal carina itself on a base of smaller size, separated from the rest of the tracheal wall (Fig. 3). The tumor rested on the carina in such manner that its most acute extremity was directed toward the right bronchus, into which it penetrated for a short distance. Distal to it was a blood clot which obstructed the lumen. The blunt extremity of the tumor passed the mid-line of the trachea on the left side and seemed to present an obstruction, moderate in degree, to the left bronchus.

Microscopic Examination.—Different sections reveal regional variations in structure of such nature that incomplete study might lead to error. In the peripheral zone the tumor tissue is seen to be loose, approaching mucoid in character. In other zones, in contrast, a fascicular structure is seen, as in a fibroma. In still other regions the structure of an osteofibroma is encountered. Finally in some parts a large number of multinuclear cells of the myeloplax type are seen, intimately mingled with all of the several structures named. This character of myeloplaxoma is without question the most constant and extensive and is to be considered basic. The other structures are only histologic variations due to mechanical conditions (mucoid structure) or to healing tendencies (structure of fibroma or osteofibroma).

This conclusion is substantiated by investigation of the histogenesis of the tumor. In fact the diagnosis of giant cell tumor implies one of

Fig. 3.—Trachea, opened through posterior wall with tumor exposed in situ.

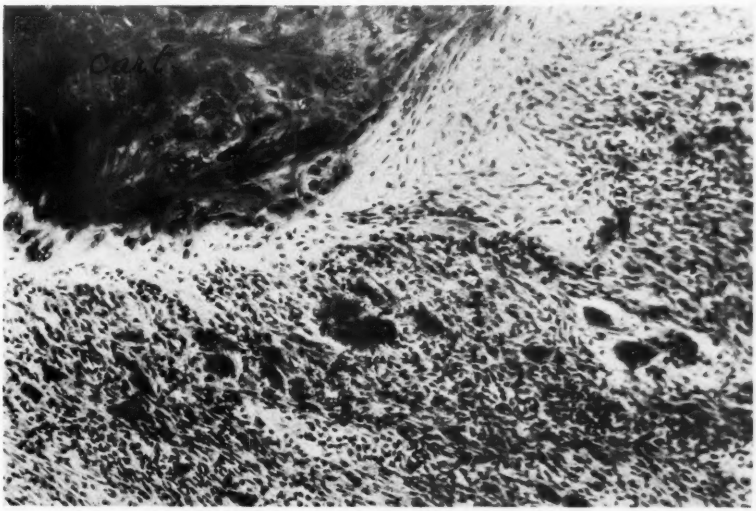

Fig. 4.—Surface of cartilage with developing ossification, osteoid tissue, and giant cell tumor.

granuloma from bone absorption (Geschickter and Copeland[8]). But since a lesion of this character is difficult to reconcile with the tracheal localization, not having been reported up to now, it was imperative to study the base of the growth on the tracheal carina to confirm the diagnosis and explanation of histogenesis. In serial sagittal sections a process of ossification is found at the lower border of one of the tracheal cartilages. This is of small size but typical and evidently the source of the tumor (Fig. 4). At the level of the tumor the cartilage shows a zone of hypertrophy; in other places the cartilage is transformed by ossification. In contact with the cartilage is a mantle of osteoid tissue upon which lie numerous osteoblasts. Further away are layers of osteoid tissue encompassed by osteoblasts. Along the inferior border of the cartilage, in which the process is most advanced, both osteolysis and osteogenesis are evident. Separating from the surface of the ossification a granuloma is in the process of formation, making up the tumor, which has grown in the form of a polyp lifting up the tracheal mucosa so that it is reflected over its own surface.

We shall not enter upon details of the histology of the lesion, except to note that the giant cells present the classic structure, typical both in shape and abundance of nuclei. These cells are found more or less dispersed and also in frequent accumulations.

As to their genesis, it is evident that they result from neighboring cells through nuclear proliferation and cytoplasmic fusion, responsible for their double plasmodial and syncytial character. Their osteoclastic function is equally apparent.

The other cells of the tumor are seldom small and rounded as encountered typically. Rather they exhibit a great tendency to become fusiform and elongated and arranged in bundles. The giant cells gradually disappear. The zones with osteogenesis reveal layers of osteoid tissue which are in a process of gradual calcification. Osteoblasts are numerous, corresponding to the predominance of osteogenesis over osteoclysis.

Diagnosis.—Ossification of the terminal tracheal cartilage. Giant cell tumor (polymorphous benign myeloid sarcoma).

Its extraordinary rarity gives special interest to this case. A search of the literature indicates that it is the first time that a giant cell tumor of the trachea has been described. D'Aunoy and Zoeller, in an exhaustive review of the literature up to 1929, have noted in summary 261 cases of benign or malignant tracheal tumors, but none of the type here described. We have not been able to find the record of any similar case after that date.

The rarity is explained by the fact that the giant cell tumor is a bone tumor, and the trachea, as Maximow and Bloom[6] note, does not tend to ossify, even in advanced age. The proof of tracheal ossification in our

case is unusual and justifies report of this tumor, for which an osseous point of departure is a "sine qua non."

The supposed benign nature of such a tumor we believe to be questionable. Chevalier Jackson maintained that "benign as applied to a growth in the tracheobronchial tree is not synonymous with innocent, inasmuch as such a growth may cause death primarily by asphyxia or secondarily by the suppurative disease caused by its obstruction to ventilation and drainage." In the special case of giant cell tumor all of these conditions would probably be aggravated by its natural character. We cannot speak with certainty because of lack of previous experience, but the following comment by Ewing,[7] referring to the usual localization of these tumors, will give an indication of the possible significance of such a tumor growing in the tracheobronchial lumen.

"The giant-cell tumor is a low-grade neoplastic process, usually single, sometimes multiple, affecting mainly the epiphyses of the long bones, but appearing in almost any bone of the body, producing a multicystic excavation with widening of the shaft, and pursuing a prolonged and generally progressive course, but failing to yield metastases. Spontaneous cure is sometimes observed, but the natural termination is death from hemorrhage and infection, after the growth has reached large dimensions and caused much destruction of bone."

We wish to express our thanks to Dr. Esmond R. Long of the Henry Phipps Institute, Philadelphia, for translating this article from Spanish.

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METASTATIC CARCINOMA OF THE LUNG INVADING AND OBSTRUCTING A BRONCHUS

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METASTATIC implants of carcinoma throughout the lung are, of course, very common, but apparently single metastatic nodules invading and occluding a main bronchus are rare. The only reports found in the literature are two of hypernephroma, metastatic to the lung with ulceration and invasion of bronchi, diagnosed bronchoscopically. These cases have been reported by Vinson and Martin[1] and Maytum and Vinson.[2] Because of its apparent rarity, the following case is reported.

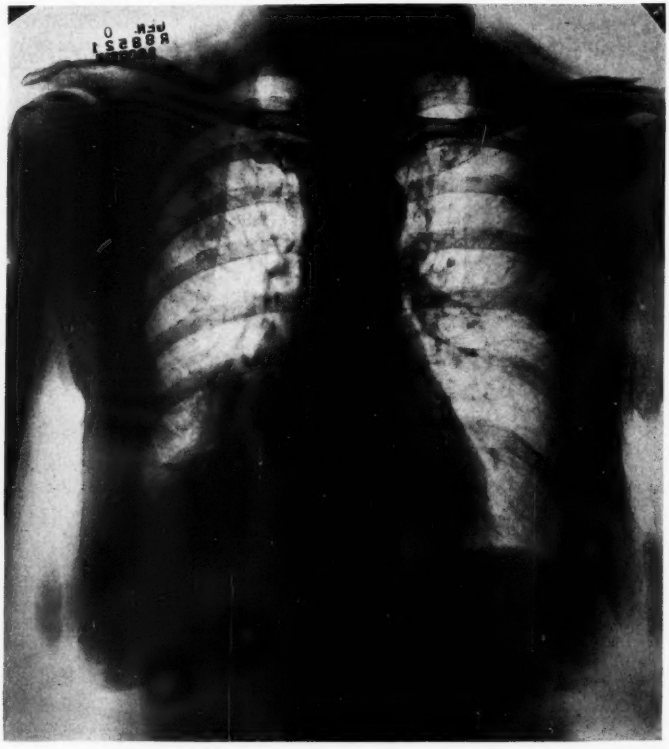

Fig. 1.—Film shows increased density in middle and lower lobes.

From Marquette University, Milwaukee.
Received for publication Jan. 14, 1941.

A white woman, aged 59 years, was admitted to the Milwaukee County Hospital on Aug. 27, 1940. Her family history was of no particular significance. Her past history revealed relatively good health until January, 1939. At that time, for an obstructive small annular carcinoma of the sigmoid, she had a one-stage abdominoperineal resection. She remained entirely well until October, 1939, when she developed a cough which persisted and increased in severity until her entrance into County Hospital. She had occasional moderate hemoptysis and began having night sweats in May, 1940. After her admission she ran a moderate persistent fever. She lost approximately 40 pounds in weight from October, 1939, to September, 1940. At no time did she have any pain in her chest. Her gastrointestinal symptoms had entirely subsided after her abdominoperineal resection.

Fig. 2.—Lung cut open after removal showing large metastatic carcinoma invading bronchus.

She was having no symptoms of indigestion and no abdominal discomfort. Physical examination revealed a thin woman whose skin was clear. She was not jaundiced. There was no cervical adenopathy. Her chest expansion was reasonably good; no râles were heard, but the breath sounds in the right base posteriorly were diminished. Her abdomen was flat. There was a colostomy in the left lower quadrant. The liver was not enlarged, and no nodules could be felt. There was no

abdominal tenderness. X-ray examination showed a normal left lung. The right lung showed some increased density in the middle and lower lobes near the hilum. No other nodules could be seen in either lung field (Fig. 1).

Bronchoscopic examination revealed that the carina was sharp and of normal appearance and motion. Just below the orifice of the upper lobe bronchus on the right side, a large papillary mass filled the lumen. Biopsy showed adenocarcinoma.

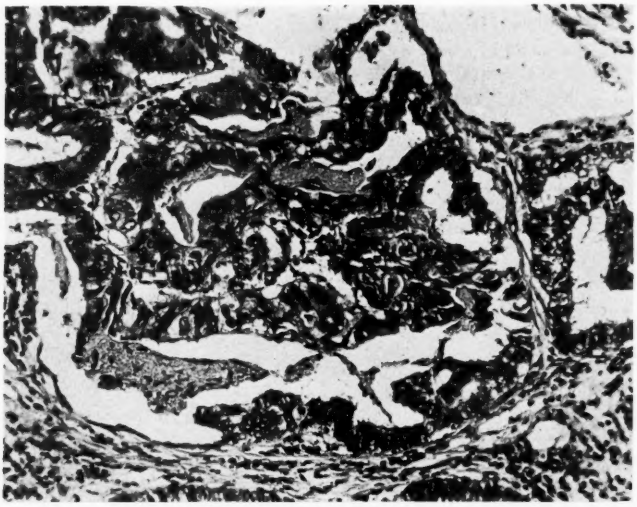

Fig. 3.—Photomicrograph showing tissue typical of adenocarcinoma of colon.

In spite of the likelihood that this lesion was metastatic from sigmoid, there could be some question that it might be primary in the bronchus. Because there were no other apparent areas involved in the lung, none that could be demonstrated in the liver and no evidence of local recurrence, a right pneumonectomy was done Oct. 14, 1940, after preliminary collapse by pneumothorax.

Convalescence was relatively uneventful with primary healing of the chest and bronchus.

Pathologic examination of the removed lung showed an oval mass penetrating the main bronchus beneath the upper lobe bronchus measuring 1½ by 2 by 1 cm. There was a small nodule near the base of the lower lobe. Microscopic examination revealed typical adenocarcinoma similar to those seen in carcinoma of the colon.

At the present time the patient is developing some gastric distress and presumably has metastasis near the liver.

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DIAPHRAGMATIC HERNIA WITH PENETRATING ULCER OF HERNIATED STOMACH

A Case Corrected by Surgery

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Louisville, Ky.

CASE REPORT

A 57-year-old, unmarried, colored male, was admitted to the Louisville City Hospital for the first time on August 31, 1939. Three nights previously he had been awakened from sleep by abdominal discomfort and swelling, dyspnea, and aching pain in the left chest, shoulder, and arm. These complaints, together with hiccough, nausea, and frequent vomiting persisted until the time of entry.

The patient had had a penile sore fifteen years before and had been receiving intragluteal bismuth injections for the previous two years. Also, four years previously he had been shot through the left chest but recovered uneventfully. The patient's past record was otherwise not remarkable. He was a healthy man, free from other complaints.

Physical examination revealed a well-developed and well-nourished negro, moderately dyspneic, and belching every fifteen to thirty seconds. Blood pressure was 134/100; pulse rate, 80. His pupils were small and equal and reacted sluggishly to light. Knee and ankle jerks could not be elicited. Chest expansion was normal, but there was dullness to percussion on the left from the eighth rib down posteriorly and tympany from the fifth rib down anteriorly. Over the same areas there was absence of whispered voice and tactile fremitus. Examination of the abdomen revealed only tenderness to deep palpation in the epigastrium.

There was a trace of albumin and occasional R.B.C. and W.B.C. in the urine. The leucocytes numbered 19,000 with 65 per cent polymorphoneuclears. The Kahn reaction was positive.

Under a presumptive diagnosis of coronary occlusion, an EKG was taken, which showed QRS_2 slurred, QRS_3 notched, small and inverted, and left axis deviation, a tracing not suggestive of fresh coronary occlusion. A roentgenogram of the chest (Fig. 1) showed an abnormally elevated left hemidiaphragm with slight displacement of the heart to the right. The true significance of these x-ray findings was not appreciated at this time. For the first fifteen hospital days the patient belched and vomited repeatedly, frequently raising small quantities of fresh blood or coffee ground material. A gastrointestinal series (Fig. 2) taken after the vomiting subsided showed an apparent herniation of the fundus of the stomach through the left diaphragm. A barium enemia revealed that the colon was not present in the herniation. In view of the hematemesis and the persisting soreness in the patient's left shoulder, an operation was advised, but the patient refused and shortly thereafter left the hospital.

From the Department of Surgery, University of Louisville School of Medicine and Louisville City Hospital.

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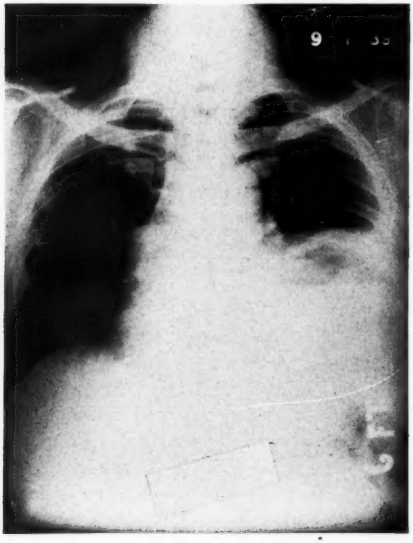

Fig. 1.—Sept. 1, 1939. High elevation of the left diaphragm with gas bubble in the fundus of the stomach is shown.

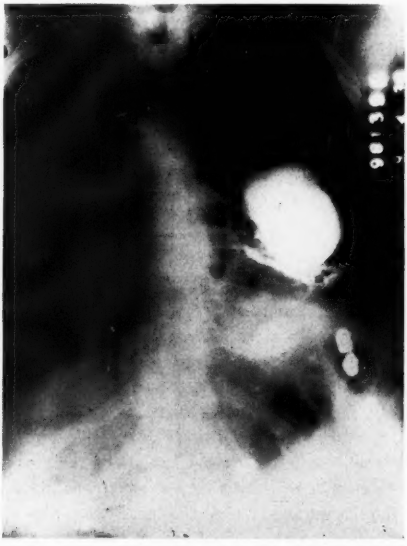

Fig. 2.—Sept. 14, 1939. Herniation of the fundus of the stomach through the left diaphragm is evident. Barium enema failed to reveal the presence of the colon in the herniation.

Fig. 3.—May, 1940. Herniation of the stomach still exists, and there is now a large penetrating ulcer of the stomach within the thorax.

Fig. 4.—May, 1940. The left half of the transverse colon is also herniated into the chest and is dragging the hepatic flexure to the left.

On November 26, six weeks following discharge, the patient was readmitted, this time to the psychiatric ward because of a convulsive seizure followed by a period of mental confusion and hallucinations. The attack was not repeated, and the patient soon became rational and normal. His spinal fluid was found to be Kahn negative. The patient was considered too poor a risk for surgical repair of his diaphragmatic hernia. The persistent left shoulder pain, now the only remaining symptom, was relieved by excision of 1.5 inches of the left phrenic nerve, and the patient was discharged.

Five months later, May 13, 1940, the patient was again admitted because of severe attacks of pain around the left lower chest. Also, he complained of gas pains relieved by sudden passage of flatus. Repeated barium studies (Figs. 3 and 4) revealed that there was now a large penetrating ulcer extending backward and mesially from the lesser curvature of the herniated fundus and that the transverse colon had also pushed up through the diaphragmatic defect into the thorax. The repair of the hernia was now considered imperative, and a transthoracic approach was decided upon because of the complicating ulcer and adhesions.

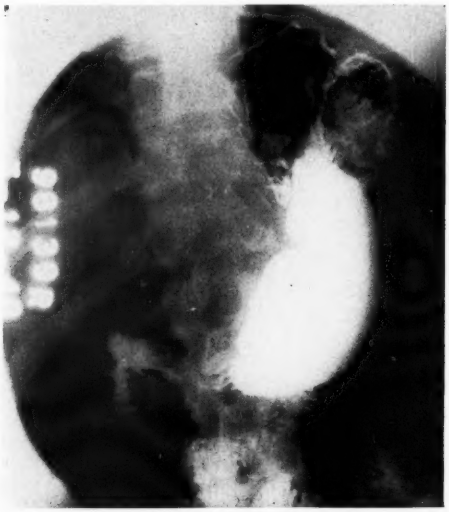

Fig. 5.—July, 1940. A study made after operation shows prominent rugae in the fundus. The stomach is now entirely below the diaphragm.

As a preliminary to operation, the left lung was collapsed by pneumothorax. Complete emptiness of the stomach was assured by an indwelling Levine tube. The patient was also placed upon cortate (desoxycorticosterone acetate) as suggested by Perla and others[1] as a prophylactic against surgical shock.

On June 25, 1940, under positive pressure cyclopropane anesthesia, surgical repair of the diaphragmatic defect was carried out through a left thoracic approach, resecting the left sixth rib from its neck to its sternal attachment, incising the pleura through its bed, and widely spreading this cleft. The lung was completely collapsed against the spine, allowing excellent exposure. The fundus of the stomach, transverse colon, and omentum were found protruding, without any

covering or sac, into the chest cavity through an oval aperture in the left leaf of the diaphragm. This defect, 3.5 inches in length, extended from just to the left of the esophageal hiatus, anterolaterally, to within 2.5 inches of the chest wall. The diaphragm, although apparently paralyzed, showed little or no atrophy. The colon and omentum were free of attachments and were therefore easily returned to the abdominal cavity. The stomach, however, was densely adherent to the diaphragm, the pulmonary ligament, and the aorta. In the midst of these adhesions the penetrating ulcer, ⅞ inch in diameter, had burrowed its way from the lesser curvature of the stomach into the outer coat of the aorta. By blunt dissection, all adhesions except those between ulcer and aorta were broken. Since it was impossible to peel the ulcer away from this great vessel, the stomach was trimmed away from the adherent crater and the resulting defect was closed in two layers. The stomach was returned to the abdominal cavity, and in the defect in the diaphragm was closed without tension by overlapping the mesial by the lateral margin with a double row of interrupted silk sutures. A rubber catheter was placed to the bottom of the costophrenic sinus through a stab wound, and the chest wound was closed. The patient underwent the 3½-hour ordeal without mishap other than a period of shock near the close of the operation. During and immediately following the operation the patient received 1,000 c.c. of citrated blood, and within eight hours the blood pressure had stabilized in the vicinity of 120/90.

Convalescence was uneventful, and the patient was discharged on July 12, seventeen days postoperative, with the wound well healed. A barium study of the stomach the day before discharge (Fig. 5) showed it to be in normal position and with but slight irregularity and irritability of the fundus. The patient was last seen in September. He was free of complaints, and his wound was healed solidly.

DISCUSSION

Fifteen years ago, Hedblom[2] collected 378 cases operated upon for diaphragmatic hernia. Now the operation is relatively common. However, in a cursory review of the literature we have found no previous case in which a penetrating gastric ulcer had to be resected along with the repair of the diaphragm.

Diaphragmatic hernias are divided by Woolsey[3] into three groups.

1. *Congenital herniation through a hiatus left by incomplete fusion of the primitive components of the diaphragm.* Such defects occur on either side posteriorly, the so-called foramina of Bochdalek and anteriorly in a parasternal location, the foramina of Morgagni (Fig. 6). Rarely the whole left half of the diaphragm is absent. Since these deficiencies involve peritoneum as well, there will be no hernial sac, thus constituting false hernia.

2. *Acquired hernia, in which stomach and occasionally other viscera push up through a lax esophageal hiatus.* These hiatus hernias are covered with a true sac of peritoneum.

3. *Traumatic hernias.* The left leaf of the diaphragm unprotected by liver may be split, either by a missile or by sudden increase of intra-

abdominal pressure. Here again, the herniating viscera will not possess a sac. The aortic and caval hiati are rarely, if ever, the site of hernia (Woolsey[3] and Donovan[4]).

The situation of the diaphragmatic defect in our case (Fig. 6) makes trauma (i.e., the bullet wound) the only likely cause. Traumatic hernias, as exemplified by this case, may not manifest themselves for several years following injury.

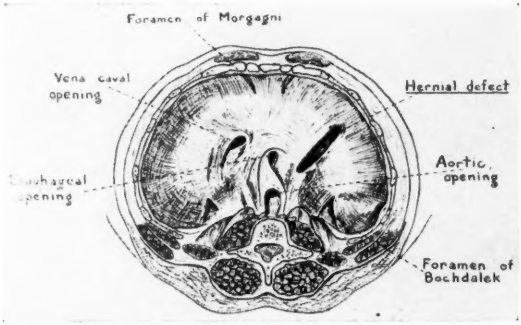

Fig. 6.—The diaphragm as seen from below (from Homans, John: Textbook on Surgery, ed. 5. Courtesy of Charles C Thomas, Publisher, Springfield). Figure shows openings through which congenital diaphragmatic hernias usually occur. The opening marked *hernial defect* locates the position of this diaphragmatic hernia.

Symptoms produced by diaphragmatic hernia may simulate coronary disease, cholecystitis, or peptic ulcer. Hematemesis from pinching and erosion of the imprisoned stomach, as occurred in our case, is not uncommon. Acute intestinal obstruction is always a threatened complication when bowel is caught in the hernia. A varying amount of dyspnea and cyanosis, especially in children, may be produced by the embarrassment of lung and mediastinum by the herniation. The assumption of certain postures sometimes will relieve the symptoms. Our patient illustrates both the phrenic and the intercostal reference of diaphragmatic pain. Interruption of the phrenic nerve relieved the shoulder and upper arm aching. Later, a half circle of pain around the left costal margin indicated irritation transmitted through the intercostal nerves from their branches that supply the periphery of the diaphragm. We are unable to explain why, after resection of 1.5 inches of the phrenic nerve six months previously, there was little or no evidence of diaphragmatic atrophy. The phrenic nerve had been exposed for several inches; accessory branches had been searched for and not found; and immediate relief of shoulder pain occurred upon section of the nerve. Incidentally, the fluoroscope revealed a motionless left diaphragm even before the phrenic resection. Could it be possible that the intercostal

innervation might be acting in a compensatory manner? One of us (L. W. F.) years ago did an avulsion of the phrenic nerve for the treatment of pulmonary tuberculosis, and the accessory nerves were divided as well as the nerve to the subclavius muscle. In this case no paralysis of the diaphragm occurred. The patient was operated upon again, and the stump of the phrenic nerve was found. Accessory phrenic nerves were searched for, and none were found. It was our opinion that this patient had received diaphragmatic innervation through the intercostal nerves as well as through the phrenic nerves. The final diagnosis of diaphragmatic hernia is made roentgenologically after the barium meal and enema. The fluoroscopy with the patient's head tilted up and then down gives valuable information as to how adherent the herniated viscera are within the thorax.

Hiatus hernias should be treated symptomatically in most cases, since the stomach is usually the only viscus involved and it is too thick walled and powerful to become obstructed or strangulated. Congenital and traumatic hernia should be corrected surgically. This indication is absolute if bowel is included in the hernia because of the danger of obstruction. The operative mortality is doubled when obstruction supervenes.

The surgical approach is under some dispute. Harrington[5] prefers to work from the abdominal side in most cases. Hedblom found a slightly lower mortality and considerably fewer recurrences when the thoracic approach was used. It seems logical, as proposed by Woolsey, that, when adhesions are suspected, a direct attack through the thorax is better, whereas for anteriorly located parasternal herniations and for most hiatus hernias an abdominal approach would be preferable. At times a combined attack may be necessary.

Our patient received pneumothorax several days before operation. This assured good collapse of the left lung and also helped to accustom him to the opening of the thorax. Although Truesdale[6] cautions against atrophy of the diaphragm from phrenectomy, there was none evident in our patient six months after resection of the phrenic nerve.

Increasing use is being made of cortical hormone as a prophylactic against surgical shock. One wonder what share the cortate therapy had in the satisfactory reaction of this patient to his long and shocking operation.

SUMMARY

1. A case of traumatic diaphragmatic hernia with penetrating intrathoracic ulcer of the stomach, relieved by surgery, is presented.

2. Diaphragmatic hernia is briefly discussed.

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THE BILATERAL SURGICAL COLLAPSE OF PULMONARY TUBERCULOSIS

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A DETAILED study of thirty-four patients with pulmonary tuberculosis treated with bilateral surgical collapse is presented in this paper. The type of case, extent of disease, measures employed, radiological and clinical results in each are reviewed. The future status of each patient and his ability to carry on his life and place in the community are also estimated.

The cases are divided into groups according to the combination of collapse measures employed; special emphasis is placed on the major surgical procedures and on how they are tolerated. Collapse on the initial side was by intrapleural pneumothorax, phrenic nerve interruption, paraffin pack, or extrapleural thoracoplasty, and in every instance a major surgical collapse was applied to the second side complementing the previously instituted and continuing collapse on the initial side. The cases presented are consecutive, gathered over a five-year period and not specially chosen from a larger series.

REVIEW OF REFERENCES

During recent years numerous authors have published series of cases reporting the various combinations of bilateral collapse therapy. In reviewing these reports, Graham and his associates[1] in *Surgical Diseases of the Chest* (1935) found that most of them had emanated from European sources. Bilateral phrenicectomy was reported in a total of eight cases with satisfactory results in only three. Cohen and Willauer[2] reported eleven cases of attempted bilateral nerve interruption with definite improvement in six cases. Two were not completed; in the other three the disease progressed and they died eventually. Schwatt[3] reported a single case only. He regarded this procedure as hazardous, particularly if performed as a permanent measure on both sides. In a report of a large series (152) of bilateral pneumothoraces, Potter[4] incidentally included twenty-eight patients with various types of combined collapse therapy, where pneumothorax failed on one or both sides. Various combinations of pneumothorax and phrenic operations were used in fifteen, thoracoplasty combined with a contralateral pneumothorax or phrenic interruption in twelve, and bilateral thoracoplasty in one. He reported fourteen, or 50 per cent, working or ambulant, one improved, one worse and twelve dead (seven of these were early postoperative deaths). He concluded that good results are obtained in relatively few cases apart from bilateral pneumothorax. The use of bilateral paraffin packs was reported by Nissen.[5] Alexander[6] reported two bilateral paraffin packs

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in his series of 100 cases with bilateral collapse. The use of the pack operation with contralateral pneumothorax was also mentioned, but the number of cases was not given. Bilateral apical thoracoplasties have been reported by Gravesen,[7] Allen,[8] Jessen,[9] Coryllos,[10] and Alexander.[6] The latter stated that there are very few instances in which bilateral thoracoplasty is indicated in view of the possibility of substituting other more limited procedures; if the disease is too gross for these procedures, then the patient certainly would not tolerate bilateral thoracoplasty. The combination of pneumothorax on one side and thoracoplasty on the other has been used much more widely. O'Brien and his associates[11] reported a series of eighty-five cases in which there was an immediate mortality of eight, or 9.4 per cent, and a late mortality of ten, or 11.7 per cent of his series. In the living patients, cavities were closed in fifty-eight, or 76.3 per cent, and sputum made negative in fifty-two, or 68.4 per cent. In his estimation this combination is considered a justifiable and useful procedure but, of course, accompanied by extra dangers and added operative risk.

MANAGEMENT OF CASES

In every instance the operations are performed under local anesthesia alone. Moderate barbiturate hypnosis is induced during the preceding twelve hours, and our choice of anesthetic is 0.5 per cent solution of novocain. Preoperative investigation includes study of the cardiovascular, respiratory, and renal systems; to that end physical examination, metabolism tests, vital capacity, Congo red test, repeated urinalyses, and Mosenthal tests are done. A complete blood study is carried out with special regard to the von Arneth count. Bleeding and clotting times are estimated, and the blood group is determined. The postoperative care is closely supervised. Special attention is given to the limitation of opiates without allowing unnecessary pain, periodic hyperventilation with oxygen and carbon-dioxide gas during the first few days after operation, expectoration to forestall any bronchial blockage, and the immediate treatment of bronchial blockage if it occurs. This phase of the treatment in patients with low vital capacity is often the decisive factor in the outcome.

DISCUSSION OF INDICATIONS AND CHOICE OF PROCEDURE

There are certain important factors which should be considered regarding the indications for, and the application of, bilateral surgical collapse therapy.

1. The extent of disease and cavitation in each lung.—The more involved lung is always considered for initial collapse, particularly if intrapleural pneumothorax can be used. When pneumothorax fails and the disease in this lung is not progressive while that in the less involved lung is, a minor measure of collapse can be applied to the less involved side in order that the disease there may be controlled before undertaking a major form of collapse on the other.

2. Progressive, stationary, or retrogressive disease.—Progressive disease usually precludes bilateral collapse unless the minor measures prove

successful. Ideally, disease should be stationary or retrogressive for the best ultimate results.

3. The length of time that must elapse before undertaking collapse.—The opportune time for collapse therapy is seldom easy to decide. A period of observation is essential before sound judgment in this regard is possible.

4. The type of collapse which will prove most efficacious and at the same time preserve the maximum amount of functioning lung.—Any minor procedure if revocable would take precedence over a major measure, and even in the latter group such operations as extrapleural pneumothorax or extrapleural pneumonolysis with paraffin filling would, in certain instances, be preferable to an extrapleural thoracoplasty. It is very seldom that conditions warrant a bilateral thoracoplasty. It is well to repeat that intrapleural pneumothorax was tried in all of these cases before any other procedure was considered. When pneumothorax failed, phrenic nerve interruption was the next procedure of choice in some, although in disease with apical cavitation more direct collapse often was considered necessary. The introduction of extrapleural pneumothorax in recent times offers an alternative to permanent surgical collapse in a carefully selected minority of these apical cases. On the other hand, extrapleural pneumothorax is essentially the same operation as an extrapleural pneumonolysis with paraffin filling, except that, in the latter, collapse is maintained permanently by wax rather than temporarily by air. The paraffin pack has the advantage of producing a more localized collapse and thus greater preservation of functioning lung tissues. Although extrapleural pneumothorax is considered a temporary procedure and extrapleural paraffin pack a permanent one, it should be pointed out that the paraffin can be removed readily and the procedure therefore is revocable just as is the extrapleural pneumothorax. A pack also eliminates the need for repeated air refills, which often necessitate the patient's remaining a much longer period in a sanatorium or requiring expensive time and energy-consuming trips to have the pneumothorax continued. It is found that extrapleural pneumonolysis with paraffin filling is a very effective measure of collapse in small apical lesions where the extent of cavitation is limited (preferably less than 3 cm.) and where the disease can be controlled by a limited extrapleural apical separation. Extrapleural pneumothorax cannot replace extrapleural thoracoplasty in cases where a gradual collapse is essential. Gradual collapse can best be achieved by an easy-staged thoracoplasty. Large and especially superficial apical cavities cannot be collapsed by extrapleural pneumothorax or paraffin pack without definite dangers from perforation of the wall of the cavity with its subsequent train of events so often ending fatally. An advantage gained by doing an extrapleural apicolysis in combination with a thoracoplasty is that collapse can be more limited and yet be effective.

ANALYSIS OF GROUPS

Group I, one case. This patient had bilateral thoracoplasty with seven ribs removed on each side.

Group II, eight cases. The initial collapse was a thoracoplasty, and an extrapleural pneumonolysis with paraffin filling was performed on the second side.

Group III, three cases. Bilateral extrapleural pneumonolysis with paraffin filling was employed.

Group IV, one case. A thoracoplasty performed on the initial side was followed by an extrapleural pneumothorax on the second side.

Group V, ten cases. Intrapleural pneumothorax was being maintained on the first side, and a thoracoplasty was performed on the contralateral side.

Group VI, ten cases. Intrapleural pnemothorax on the initial side was followed by an extrapleural pneumonolysis with paraffin filling on the second side.

Group VII, one case. A phrenic crush repeated three times and resulting in permanent diaphragmatic paralysis was followed by thoracoplasty on the contralateral side.

ANALYSIS OF OPERATIONS

The wide choice of operations has resulted in the many varied groups. In twenty persons an initial pneumothorax was used, and in seven of these a closed intrapleural pneumonolysis was performed to improve the type of collapse and, if possible, to make it selective. Temporary phrenic paralysis was performed five times as a tentative procedure on the contralateral side, with little benefit, and had to be superseded by some major surgical procedure. On three occasions it was performed on the second side collapsed as a permanent measure and followed by the major surgical operation.

In the series of thirty-four cases, twenty-five paraffin packs were used. In all cases the extrapleural pneumonolysis before paraffin filling was limited in extent and only a small filling made. The smallest was 116 Gm.; the largest, 255 Gm. Of this group, two had to be removed later (Cases 20 and 23), one because of infection in the pack bed, the second because of failure to effect cavity closure. Each of these removals were followed by a partial thoracoplasty with satisfactory results.

Extrapleural thoracoplasty was performed on twenty-one persons with a total of twenty-two sides collapsed, and in all there were fifty-nine separate thoracoplasty stages performed. (Group I represents a bilateral case, Case 9.) The original intention in Case 9 was to do a thoracoplasty on the one side and follow with a paraffin pack on the second side, but due to technical difficulties at operation a pack was impossible, and thus a thoracoplasty on the second side was unavoidable.

In Group IV, one patient had thoracoplasty on the initial side with an extrapleural pneumothorax on the contralateral side.

A total of eighty-five major surgical operations, mainly thoracoplasties or paraffin packs, were performed on the thirty-four patients (that is, without considering the phrenic nerve operations and the closed intrapleural pneumonolyses in the pneumothorax cases).

In twenty-one persons the initial collapse was performed on the left side and in thirteen on the right side.

RADIOGRAPHIC RESULTS

In Groups I, III, IV, and VII closure was complete on both sides. These were limited in number, but even in the larger groups there was a gratifying percentage of cavity closure, the total revealing 94.1 per cent of closure on the initial side and only 5.9 per cent remaining open; on the second side collapsed there was 94.1 per cent closure of cavities with 5.9 per cent residual. In thirty-four cases there were actually thirty with complete closure of cavities on both sides as evidenced in the x-ray study. Twenty-one patients had twenty-two sides collapsed by thoracoplasty, and twenty, or 90.9 per cent, showed complete disappearance of cavity. Twenty-five extrapleural pneumonolyses with paraffin filling were done in twenty-two cases (three bilateral), and twenty-three, or 92.0 per cent, of these were successful in closing all cavitation. As previously mentioned, two unsuccessful ones were removed and replaced by thoracoplasty and cavity closure obtained in both. Twenty cases had pneumothorax; nineteen, or 95.0 per cent, showed successful cavity closure, and in one only was a small residual cavity evident. The solitary extrapleural pneumothorax included in this series was sufficient to close a large (5 cm.) hilar cavity. Finally, in Group VII, phrenic nerve interruption with permanent diaphragmatic paralysis proved effective in closing cavitation in one case.

CLINICAL RESULTS

The clinical results in this series are not definitely conclusive as the cases have not been followed for a long enough period. The longest time that any patient in the series was followed was slightly over four years, and the shortest time was six months.

Group I, with only one person, shows 100 per cent arrested with no mortality.

Group II, including eight cases, shows one apparently cured carrying on at home and working, four arrested or apparently arrested but still in the sanatorium, two improved with only an occasional concentrated sputum positive. In only one is there no improvement shown as a result of bilateral collapse.

Group III includes three cases. Two are apparently arrested but still in the sanatorium; one is quiescent. Sputum has been rendered negative in all three.

In Group IV only one patient is included and disease is satisfactorily controlled and considered quiescent.

In Group V, ten cases are studied. One patient is apparently cured and working; three cases are arrested; one patient is carrying on at home. In two, disease is considered quiescent, and the remaining four show definite improvement, although one still has positive sputum and another has occasional positive sputum.

Ten cases are reviewed in Group VI of the group. Six cases are arrested; five patients are carrying on at home, and two of these are working. Three show definite improvement, although only two are consistently negative; one has occasional positive sputum; and one patient died following a large hemorrhage into the area of the pack on the sixth postoperative day.

The final group included only one patient in whom disease is arrested, and she is carrying on at home at her usual work.

Thus there was only one death, this being an early postoperative occurrence. There are nineteen, or 55.9 per cent, in whom the disease is either apparently arrested, arrested, or apparently cured. Of this group, six, or 17.6 per cent, are able to work and carry on a practically normal existence. In another four, disease is considered quiescent; nine have been improved definitely by the operation. Thus 94.2 per cent are classified as improved or better as a result of the bilateral collapse. Only one, or 2.9 per cent, has continued unimproved by the surgical measures employed. Actually twenty-seven, or 79.4 per cent, of the thirty-four patients have negative sputum by the various methods of examination used which include smear, concentration of sputum, cultures of sputum, and gastric intubation with examination of the stomach contents for bacilli. A subsequent report on these cases is contemplated as well as the addition of further material.

SUMMARY

1. A series of thirty-four consecutive cases of bilateral collapse is discussed including seven different combinations of major and minor surgical procedures.

2. In twenty-three, or 67.6 per cent, disease was far advanced and in only eleven, or 32.4 per cent, moderately advanced.

3. Results of operation indicate that 55.8 per cent were considered apparently cured, arrested, or apparently arrested, and 17.6 per cent of the group are working. In all, twenty-seven, or 79.4 per cent, were sputum negative at the time of this study.

4. The mortality rate of 2.8 per cent in this group of patients, many of whom were considered extremely doubtful operative risks, is most gratifying.

CONCLUSION

Bilateral pulmonary collapse by major surgical measures is a useful procedure and offers hope to cases that would otherwise have to be regarded as hopeless or, at best, destined to years of chronic invalidism.

The varied combinations of collapse measures increase greatly the resources of the phthisiologist. As recently as ten years ago there was little more than bed rest with pneumothorax and phrenic operations that could be offered the patient with bilateral pulmonary tuberculosis disease. Today we have an armamentarium which can cope with a large percentage of these sanatorium problems.

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The Rose Lampert Graff Prize competition will be held again this year and is open to any licensed physician in the United States or Canada. The prize is awarded to the paper judged by the Prize Committee to be the best submitted to them prior to Feb. 1, 1942, and dealing with a subject related to diseases of the chest regardless of whether it is anatomical, physiological, or clinical. The length of the paper should be such as to make it suitable for publication in THE JOURNAL OF THORACIC SURGERY.

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